5-2014

New Synthetic Methodologies for Chemo-, Stereo-, and Regioselective 1,4-Conjugate Additions of Organometallic Reagents to Michael and Extended Michael Substrates and Alkene Halofunctionalization Reactions

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NEW SYNTHETIC METHODOLOGIES FOR CHEMO-, STEREO-, AND REGIOSELECTIVE 1,4-CONJUGATE ADDITIONS OF ORGANOMETALLIC REAGENTS TO MICHAEL AND EXTENDED MICHAEL SUBSTRATES AND ALKENE HALOFUNCTIONALIZATION REACTIONS

A Dissertation Presented to
the Graduate School of
Clemson University

In Partial Fulfillment of the Requirements for
the Degree of Doctor of Philosophy
Chemistry

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by
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May 2014

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ABSTRACT

The research discussed in this dissertation is focused on developing new synthetic methodologies for the construction of carbon-carbon and carbon-heteroatom bonds present in several natural products and synthetic intermediates employing organometallic reagents and/or organocatalytic procedure. The presence of rich functionality in the reactive synthons under study provides opportunities for studying a variety of reactions. Effecting a reaction in a regio- and stereoselective fashion is highly attractive as the resulting synthons can be used for the syntheses of larger molecules. We have explored unprecedented variation of Michael Initiated Ring Closure (MIRC) reactions for the syntheses of 1,2,3-trisubstituted cyclopropane derivatives, owing to their numerous applications in several fields involving synthesis of natural products, agrochemicals, pharmaceuticals and flavor/fragrance additives via the reaction of γ,δ-epoxy Michael substrates (e.g., epoxyenoates, epoxyenones, epoxyensulfones and epoxyenamides) with organozincate reagents under the conditions catalytic or stoichiometric in the zinc(II) salts. The diastereoselectivity of a cyclopropanation reaction is dependent upon the solvent employed for alkyl Grignard reagents reacting with epoxyenoates, ensulfones, and enamides but solvent independent for reaction with enones. Excellent diastereoselectivity can be achieved for the epoxy enoates, enones, and ensulfones while the enamides afford modest diastereoselectivity even under optimal conditions. The MIRC adduct can be achieved with phenylmagnesium bromide under the specific reaction conditions designed to minimize the biphenyl formation. The newly developed protocol can also be extended for the diastereoselective cyclopropanation reaction of organozincate reagents with γ-haloenoates.

The next application of our new methodologies is to seek a regioselective 1,4-conjugate addition reaction of Grignard reagents to nitrodienes in the presence of Zn(II) salts. The fine-

tuning of reaction conditions and employment of a wide range of ligands such as alkyl, aryl, heteroaryl, allyl, vinyl, 1-alkynyl, alcohols and alkyl thiols gave regioselective 1,4-conjuagte addition products in excellent yields. The newly discovered methodology can also be used for the regioselective 1,4-conjugate addition reaction to 2,4-hexadienethiolate.

In addition, we made progress in developing new synthetic methodologies for halofunctionalization of alkenes promoted by chiral organocatalyst. Several amidines and Schiff bases effectively catalyze the *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) promoted haloacetoxylation or haloetherification of alkenes and halolactonization of unsaturated acids in high yield (56-97%) and high diastereoselectivity (95:5-100:0 dr). Our investigation confirmed that the carbon nitrogen double bonds of amidines or Schiff bases acted as efficient catalyst for the transfer of halonium (usually bromonium or iodonium) ion from halogen sources to alkene. Several nucleophilic species such as anions of alcohols, alkyl thiol, benzyl thiol and methane sufonic acid were successfully employed for the bromofunctionalization reaction. Our continued effort in exploring new organocatalysts, imidazolium salts, chiral phosporamidite and chiral diphenylprolinol silyl ether were explored as new entries for the stereoselective halofunctionalization reactions.

The piperidine ring is an important structural subunit of many naturally occurring alkaloids and pharmaceutical products. In pursuit of a catalytic asymmetric approach to substituted piperidines or piperidinones, the conjugate addition reaction of Grignard reagents to 4-pyridones using chlorotrimethylsilane or borontrifluoride-diethylether as additive was explored. Copper catalysis was not required for the reaction and mechanistic rationalization suggest the conjugate addition of Grignard reagents to 4-pyridones. This new protocol can be used for the diasteromeric synthesis of *trans*-2,6-disubstituted tetrahydropyridones selectively, while cuprates give both *cis* or *trans* disastereomers or mixtures. The assignment of stereochemistry of these diastereomers is often problematic. The 1D and 2D NMR spectra of the 2,6-disubstituted tetrahydropyridones and corresponding piperidinols was investigated.

DEDICATION

This dissertation will be incomplete without acknowledging my parents Mr. Tirtha Raj Dhakal and Mrs. Goma Dhakal who pour all of their endless love, unwavering support, inspirations, and encouragement and install good foundation on me. My parents are great role model of resilience and strength. I am grateful to them who taught me the value patience, persistence and hard working for successful life. I am dedicating this dissertation to them.

ACKNOWLEDGMENTS

The completion of my dissertation and subsequent Ph. D. become a long journey due to several challenges faced during the period. Despite slow rate, with steady and rigorous effort, I finished my dissertation. Although, writing dissertation is my individual work, I reached to such pinnacle or explored the depth of scientific finding with the concerted efforts of many people around me. One of the most influential people in my academic carrier who is unselfishly willing to boost my research maturity in this level is my supervisor. It is my greatest pleasure to express sincere gratitude to Professor R. Karl Dieter for his continuous support, rigorous guidance, tutelage, encouragement, faith and confidence in me. His clear and unwavering visions has taught me innumerable lessons and insights for working in the synthetic organic lab as a bench chemist and help to brush aside frustration developed several times during the research.

I found that my life at Clemson University was sharply decorated by many dynamic and versatile groups of faculties. I want to express my sincere gratitude to all of them. My sincere thanks go to Prof. Bill Pennington, Prof. Dev Priya Arya, Prof. Rhett C. Smith and Prof. Daniel C. Whitehead for serving on my dissertation committee and providing me constructive suggestions. I want to thank for Prof. Steven Stuart and Dr. Tugba Kucukkal for theoretical calculations of a few molecular structures used in my dissertation. I am indebted to all the faculties of chemistry department particularly Dr. Alex Kitaygorodskiy for NMR help, Dr. Don Vanderveer and Dr. Collin McMillan for X-ray crystallographic help. Besides, I owe much thanks to Dr. Sean O'Connor and Mrs. Barbara Lewis for giving me the opportunity to work in the organic and general chemistry laboratories. I want to thank Mrs. Robin Wilmott, Mrs. Laura Hupp, Mrs. Heather Shelton, Mrs. Sharon Smith, Mrs. Christine Dinger and Mrs. Nicole Hodgson who helped me on several occasions throughout my research in chemistry department.

I want to thank the past and present members of Dr. Dieter's lab who were always supportive to me and provided useful suggestions on many occasions during my stay in the lab. These include Dr. Fenghai Guo, Dr. Yaxin Huang, Emmanuel Amoah, Alfredo Picado and McKenzee Campbell. Without their help, the dissertation will not be at this level.

I am indebted to my brother Dr. Pashupati Dhakal, sister in law Sangita Khanal Dhakal, sister Sharmila Dhakal and brother in law Bishnu Baral for their unconditional support, both financially and emotionally throughout my degree. In numerous ways, their support brought me through difficult circumstances. Finally but immensely, I would like to thank my wife Bina Silwal Dhakal for her continuous support, encouragement, and unwavering love. Her tolerance of my occasional stressed moods is an evidence of her continuous love and devotion. She has taken care of all family stuffs without complaining so that I could focus on completing my dissertation. She has patiently waited for several hours alone while I was working in the laboratory and on my dissertation. As for my sweet little girl, Rubisha Dhakal, my love and longing for her are beyond words. She is the softest point of my heart and cherishes my life with her presence.

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CHAPTER I

A SELECTIVE OVERVIEW OF ORGANOZINCATE CHEMISTRY

1.1 Introduction to Organozinc Reagents

The discovery and development of new synthetic methods involving organometallic reagents continues to be more important now than ever for the construction of carbon-carbon bonds.[1] Currently, the use of organometallic reagents for the construction of carbon-carbon and carbon-heteroatom bonds presents in large numbers of natural products and synthetic intermediates is one of the most studied reactions in organic chemistry.[1] In 1760, French chemist Cadet reported the first organometallic compound during the reaction of arsenic oxide with potassium acetate while synthesizing invisible ink.[2] The reaction gave a vile-smelling red liquid that was later identified as dicacodyl [$As_2(CH_3)_4$]. However the first organozinc reagent; diethylzinc was reported by Edward Frankland[3] in 1849, which was also the first compound discovered with a metal-carbon covalent bond. In 1958, Wanklyn reported the first crystalline sodium/potassium trimethylzincate reagents.[4] Organozinc and organozincate reagents were widely used for the construction of new carbon-carbon bonds until the discovery of organomagnesium reagents by Grignard in 1900.[5] In the earlier days, the extreme sensitivity of organozinc and organozincate reagents toward moisture and oxygen limited their applicability in organic syntheses. However, after the discovery of the operating conditions, these reagents are regarded as valuable synthetic tools and have had a synthetic impact similar to or superior to other transition metal organometallic reagents with few exceptions like organocopper and organopalladium reagents in organic syntheses.[6] The organozinc reagents have more stability and more covalent character in the Zn-C bond in comparison to Li-C or Mg–C bonds of corresponding organolithium and organomagnesium

reagents. In addition, organozinc reagents are most efficient for transmetallation to palladium, compatible with a wide range of functional groups (i.e., carbonyls and nitriles) and can be prepared directly from functionalized halides (e,g., α-bromoesters), thus allowing functionality in both coupling partners.[7] The synthetic versatility of organozinc reagents is illustrated by the successful use of these reagents in the Reformatsky reaction[8] and Simmons-Smith cyclopropanation.[9] Besides, organozinc reagents[10] are increasingly used in Negishi coupling,[11, 12] Fukuyama coupling,[13] and oxidative coupling.[14, 15]

Some organometallic reagents (e.g., R_2Zn, RCu and R_3Al) have a tendency to react with anionic species and formed "ate complexes." The central metal atom in the organometallic reagents has a low lying vacant p orbitals that can accommodate up to four electrons on reacting with anionic species and form the ate complexes. Usually, ate complexes are much more reactive than their neutral counterpart. Hence, monoalkyl and dialkyl zinc reagents are less reactive hence require additives[16] for reactions. These reagents also undergo transmetallation to transition metals (e.g., Pd, Cu, Ni, Ti, Zr) and promote a variety of organic transformations.[16-18] Organozincates,[19] due to their highly reactive nature, mediate epoxide openings,[20] 1,2-addition to carbonyl,[21] 1,4-conjugate addition to the Michael substate,[22] benzyne formation,[23] *ortho*-metallation,[24] cross coupling,[25] and anionic polymerization[26] reactions even in the absence of additives. Although, organozincates behave similar to organocuprate reagents in conjugate addition or epoxide openings reactions, the mechanism is quite different. Zn(II) and Cu(I) are isoelectronic configurations with filled 3d subshells however due to the higher effective nuclear charge in Zn(II) ion compared to Cu(I) ion, organic part of organozincates behaved as alkyl/aryl nucleophile while copper-atom itself acts as nucleophile in the organocuprate reactions.[27, 28]

1.2 Pioneering Studies

The pioneering syntheses of diethylzinc was reported by Edward Frankland in 1849 via the oxidative addition of iodoethane to dispersed zinc which was later named as Rieke zinc.[29]

$$2EtI + 2Zn \longrightarrow Et_2Zn + ZnI_2 \qquad (1)$$

In 1858, Wanklyn[4] reported the syntheses of crystalline sodium/potassium triethylzincate reagents by the reaction of diethyl zinc with sodium metal.

$$3Et_2Zn + 2Na \longrightarrow 2[Et_3Zn]Na + Zn \qquad (2)$$

$$3Et_2Zn + 2K \longrightarrow 2[Et_3Zn]K + Zn \qquad (3)$$

The physical and chemical properties of trialkylzincate were first investigated by Hein[30] in 1922. Wittig[31] used Ph_3ZnLi and Ph_3MgLi reagents for organic syntheses. In 1958, Wittig coined the term "ate" for a compound having anionic formulations formed in the reaction of Lewis acid with Lewis base where the central atom increases its valence.[32] In the meantime, Jander and Fisher[33] reported a concentration-dependent conductance of the association complex (i.e., Et_3ZnLi) generated in the reaction of ethyl lithium with diethyl zinc that dissociates into Li^+ and $[ZnEt_3]^-$ ions in solution. This result confirmed the presence of lithium triethylzincate during the reaction of EtLi with Et_2Zn. The structural analysis of the these reagents in solution also supported the earlier result where organozincates existed as contact ion pairs (CIP) or solvent separated ion pairs (SSIP) with metallic cation and zinc centered anions.[19] Waack and Doran[34] calculated the bond energy, stoichiometry and association constant of the complex generated during the reaction of 1,1-diphenyl-1-hexyllithium with diethyl zinc using spectroscopic analysis. ^7Li and ^1H NMR analysis of the complex generated in the reaction of MeLi with $ZnMe_2$ in diethyl ether suggested the presence of higher order zincates such as Li_2ZnMe_4 and Li_3ZnMe_5.[35] The

formation of tetracoordinate organozincates was confirmed by Weiss and Wolfrun[36] from a powder X-ray crystallographic study of Li_2ZnMe_4 where the anionic moiety has distorted tetrahedral geometry.

In 1977, Goto and coworkers[37] reported the first 1,4-addition reaction of trialkylzincate reagents to cyclic enones. In 1989, Harada and coworkers[38] reported the application of lithium trialkylzincate reagents for the bromine-zinc exchange reaction of *gem*-dibromoalkanes. After that, hundreds of experimental and theoretical papers employing organozincate reagents for the construction of carbon-carbon bonds were reported by Harada, Kondo, Mulvey, Nakamura, Suzuki, Uchiyama and Dieter's groups. The chemistry of organozincate reagents in accordance with the investigation underway in our laboratory will be briefly reviewed in this chapter of the dissertation.

1.3 Classification of Organozinc Reagents

Organozinc reagents are commonly prepared from the transmetallation reaction of organolithium (RLi) or Grignard reagents (RMgX) with anhydrous zinc salts (e.g., ZnX_2, X = Cl, Br, I, OAc, CN). Depending upon the number of alkyl groups attached to the zinc metal, organozinc reagents are classified into three types.[39]

I. Organozinc halide (RZnX). These reagents are usually prepared by the reaction of organolithium or organomagnesium reagents with zinc halide or the reaction of alkyl halide with Rieke zinc.[29,39]

$$RM + ZnX_2 \longrightarrow RZnX + MX \qquad (4)$$

$$RX + Zn \longrightarrow RZnX \qquad (5)$$

M = Li, MgX
X = Br, Cl

II. Diorganozinc (R^1R^2Zn). These reagents can be prepared by the reaction of two equivalents of organolithium/organomagnesium reagents with zinc salts where R^1 and R^2 can be same or different alkyl or aryl groups.[39]

$$R^1M + R^2M + ZnX_2 \longrightarrow R^1R^2Zn + 2\,MX \qquad (6)$$

R^1 = alkyl or aryl
R^2 = alkyl or aryl
M = Li, Mg; X = Br, Cl

III. Tri/tetraorganozincates ($R^1R^2R^3ZnM$ or $R^1R^2R^3R^4ZnM_2$). The reaction of one equivalent each of three or four organolithium or organomagnesium reagents with zinc salts gives tri- or tetraorganozincate reagents respectively.[39]

$$R^1M + R^2M + R^3M + ZnX_2 \xrightarrow[-\,2MX]{} R^1R^2R^3ZnM \xrightarrow{R^4M} R^1R^2R^3R^4ZnM_2 \qquad (7)$$

$R^1 = R^2 = R^3$ = alkyl or aryl
R^4 = alkyl, CN, SCN
M = Li, Mg; X = Br, Cl

The reactivity of the particular organozinc reagents in organic reaction is governed by the electronegativity of the ligand attached to the zinc metal and the steric in the nucleophile. A general trend for the reactivity is[39]:

Alkynyl < alkyl < alkenyl ~ aryl < benzyl < allyl

While the reactivity of different organozinc reagents is in the order of [39]:

$RZnX < R^1R^2Zn < R^1R^2R^3MgX < R^1R^2R^3ZnLi$

1.4 Preparation of Organozincate Reagents

1.41 Zincate Preparation by Ate-complex Formation

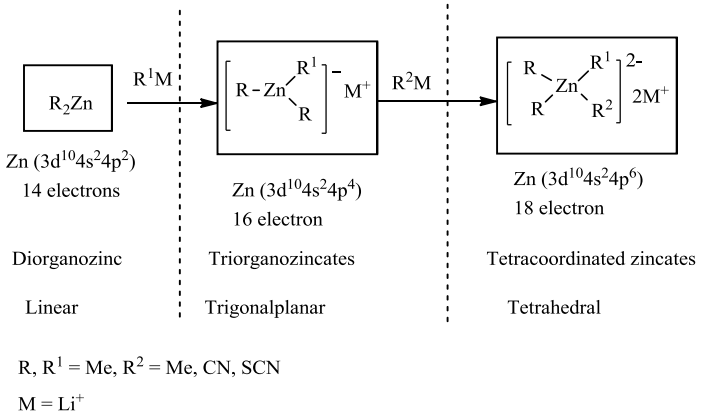
Generally sodium and potassium organozincate reagents are prepared by using the Walkyn's procedure[4] (*vide supra*). However, the common method for the syntheses of a variety of alkyl, alkenyl, aryl or silyl zincates is the transmetallation of organolithium or Grignard reagents (3.0 equiv) with ZnX_2 (X = Cl, Br, I, CN, OAc).

$$3RM + ZnX_2 \xrightarrow{THF/ether} R_3ZnM + MX \qquad (8)$$

R = alkyl, aryl, alkenyl, silyl
M = Li, MgX
X = Cl, Br, I, CN, OAc

In 1998, Uchiyama and coworkers[40] reported the syntheses of higher order organozincate reagents during the reaction of lithium trimethylzincate with methyl lithium (**Scheme 1.1**). The zinc ion in lithium trimethylzincate has 16 electrons in its outer shell and hence can undergo further reaction with anionic species such as MeLi, LiCN or LiSCN to form tertaalkylzincates and attain the inert gas configuration [i.e., 18 outer shell electrons].

Scheme 1.1 Uchiyama Model for Organozinc Reagents.[40]

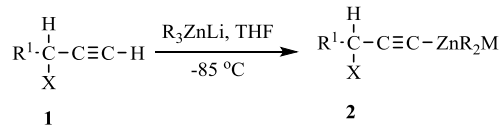


In $Me_3Zn(R)Li_2$ (R = Me, CN, SCN) reagents, methyl, cyano or thiocyano groups are directly attached to the Zn atom and showed dianionic zincate structures. The structure of newly generated organozincates was determined by ^1H NMR, Raman, in situ FTIR and extended X-ray absorption fine structure (EXAFS) studies which was in accordance with theoretical calculations.[40]

1.42 Mixed Zincates Preparation by Metallation

Despites increasing interest in organozincate reagents for the construction of carbon-carbon bonds, only one equivalent of the reagent is consumed in the reaction while the remaining two equivalents of reagent are lost during the work up process. Hence the syntheses of triorganozincate reagents from expensive ligands are usually less cost-effective process. The lack of ligand efficiency in these reagents requires the syntheses of mixed organozincate using 2.0 equivalents of inexpensive non-transferring ligands or the generation of organozincates employing procedure catalytic in zinc (II) salts. The common method for the preparation of mixed organozincate involved the treatment of one equivalent each of R^1M, R^2M, R^3M (R = alkyl/aryl group, M = Li, MgX) with ZnX_2 (X = Cl, Br,I, CN, OAc). Harada and co-workers[41, 42] reported the syntheses of mixed propargylicdialkyl zincate **2** during the reaction of propargylic substrate **1** with lithium trialkyl/arylzincate (**Scheme 1.2**). These reagents are currently used for the syntheses of a variety of allenes and propargylic derivatives.

Scheme 1.2 Preparations of Mixed Organozincates from Propargylic Substrates.[41, 42]



1 **2**

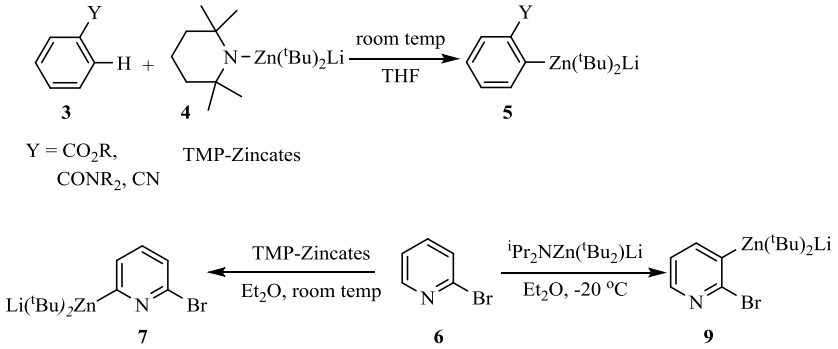
R = Me, Bu, ^{s}Bu, ^{t}Bu, Ph

R^1 = Me, $PhCH_2CH_2$, C_8H_{17}, c-hexyl

X = OMs, Cl, $OP(O)(OEt)_2$, $OCONR_2$

Kondo and co-workers[43] reported the syntheses of ortho-functionalized arylzincate **5** during the metallation reaction of functionalized benzene **3** with 2,2,6,6-tetramethyl-piperidinato(TMP)-zincate **4** (**Scheme 1.3**). The regioselective zincation of 2-bromopyridine with TMP-zincate in Et_2O at room temperature gave lithium 2-bromo-6-pyridinyl-di-tert-butylzincate (**7**) while reaction of DA-zincate with 2-bromopyridine in Et_2O gave lithium 2-bromo-3-pyridinyl-di-tert-butylzincate (**9**).[44] These functionalized reagents are currently used for the introduction of functionalized aryl and heteroaryl groups present in several synthetic targets and natural products.

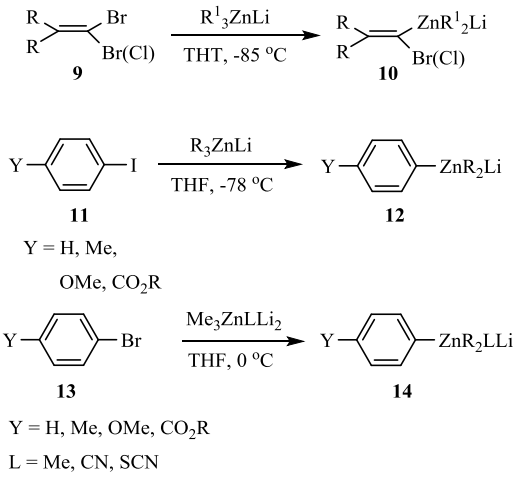
Scheme 1.3 Syntheses of Functionalized Arylzincate.[43,44]



1.43 Mixed Organozincates by Halogen Metal Exchange Reaction

Halogen metal exchange reaction of lithium trialkylzincate reagents with alkyl, alkenyl or aryl halides is one of the established methods for the syntheses of mixed organozincate reagents in organic chemistry. Harada and coworker's[38,45-47] investigation on bromine-zinc exchange reactions of *gem*-dibromoalkene **9** with lithium or magnesium trialkylzincates showed that the exchange reaction was kinetically preferred at the highly hindered bromine atom (**Scheme 1.4**). The effect was moderate for mono-substituted *gem*-dibromoalkene but higher for disubstituted *gem*-dibromoalkene. Aryl iodide usually undergo iodine-zinc exchange reaction with trialkylzincates[40] however Br-Zn exchange reaction of aryl bromide failed with trialkylzincates and needed highly reactive tetra-coordinate zincate reagents (Me_3ZnLLi_2, L = Me, CN, SCN).

Scheme 1.4 Mixed Organozincates Syntheses by Halogen Metal Exchange Reaction.[38,45-47]

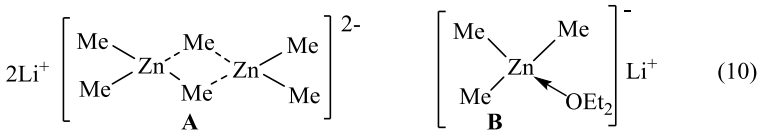


The observed reactivity of trialkyl organozincate use for the halogen-zinc exchange reactions roughly decreased in the order of $^{n}Bu \sim {}^{s}Bu > {}^{t}Bu > Me$.

1.5 Structural Study of Organozincate Reagents

Although organozincate reagents are highly valuable in organic syntheses, considerably less effort has been directed toward investigating the structural complexity of the reagent at the molecular level. In 1966, Seith and Brown reported the ^{7}Li and ^{1}H NMR analysis of the higher order zincates[35]; Li_2ZnMe_4 and Li_3ZnMe_5 and two year later, Weiss and Wolfrun[36] established the distorted tetrahedral geometry of Li_2ZnMe_4 using powder X-ray crystallography (*vide supra*). Structural evidence for the formation of $LiZnMe_3$ during the reaction of MeLi with Me_2Zn (1:1 ratio) was reported by Ashby and co-workers using IR and NMR spectroscopic techniques.[48] The infrared spectrum of the mixture in Et_2O showed absorption bands at 685 (s), 620 (s), 583 (s), 482 (s) and 425 cm^{-1}. The formation of $LiZnMe_3$ complex in the reaction was rationalized due to the presence of absorption bands at 620 and 425 cm^{-1}, which were not seen in either of the starting materials. The bands at 482 cm^{-1} and 583 cm^{-1} were assigned for υ (Li-C) vibration of MeLi and υ (Zn-C) vibration of Me_2Zn, respectively, on comparision with literature data.[49, 50] The ^{1}H NMR spectrum of the mixture of MeLi with Me_2Zn (1:1 ratio) showed a single sharp peak at room as well as lower temperatures (-86 ºC). This result suggested the existence of either a single zincate structure or the very rapid equilibrium between MeLi and Me_2Zn with corresponding zincates in the solution.

$$MeLi + Me_2Zn \rightleftharpoons LiZnMe_3 \qquad (9)$$



(10)

Rijinberg and co-workers[51] isolated the first magnesium bis(tribenzylzincate) complex (i.e., $Mg(thf)_6[Zn(CH_2Ph)_3]_2$, **15**) as colorless, air and moisture sensitive solid during the reaction of

$Mg(CH_2Ph)_2(thf)_2$ with two equivalents of $Zn(CH_2Ph)_2$ in THF. The molar conductivity of complex **15** in THF (Λ_m = 2.76 $cm^2\ \Omega^{-1}\ mol^{-1}$) had 160 times greater than that of starting materials confirming the ionic character of the solid. The ^1H NMR of **15** in deuterated benzene showed lower field methylene absorptions at δ 1.83 compared to δ 1.62 for $Mg(CH_2Ph)_2(thf)_2$ suggested the formation of new structure.

$$Mg(CH_2Ph)_2(thf)_2 + 2\ Zn(CH_2Ph)_2 \xrightarrow{THF} \underset{\mathbf{15}}{Mg(thf)_6[Zn(CH_2Ph)_3]_2} \qquad (11)$$

The structure of complex **15** was established by single crystal X-ray crystallography.[51] Complex **15** in THF or benzene gave geometrically identical crystals (i.e., **15.THF** or **15.Benzene** crystals respectively). The X-ray structure of **15.Benzene** showed packing of four $[Zn(CH_2Ph)_3]^-$ monoanions and two benzene molecules on crystallographic inversion center in the unit cell along with two separate $[Mg(thf)_6]^{2+}$ dications on crystallographic inversion center (**Figure 1.1**). **15.Benzene** had slightly distorted octagonal magnesium dication surrounded by six THF molecules along with completely separated distorted trigonal planar zincate anion.

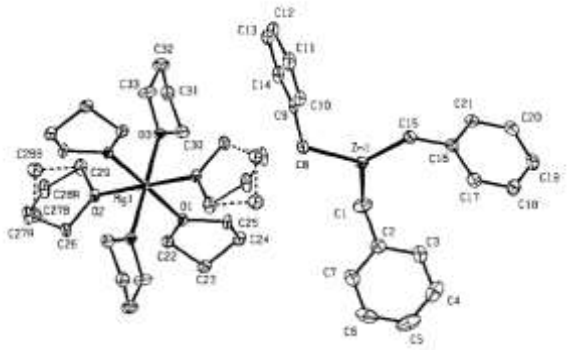


Figure 1.1 X-ray Crystallographic Structure of **15.THF** (reported with copy right permission).[51]

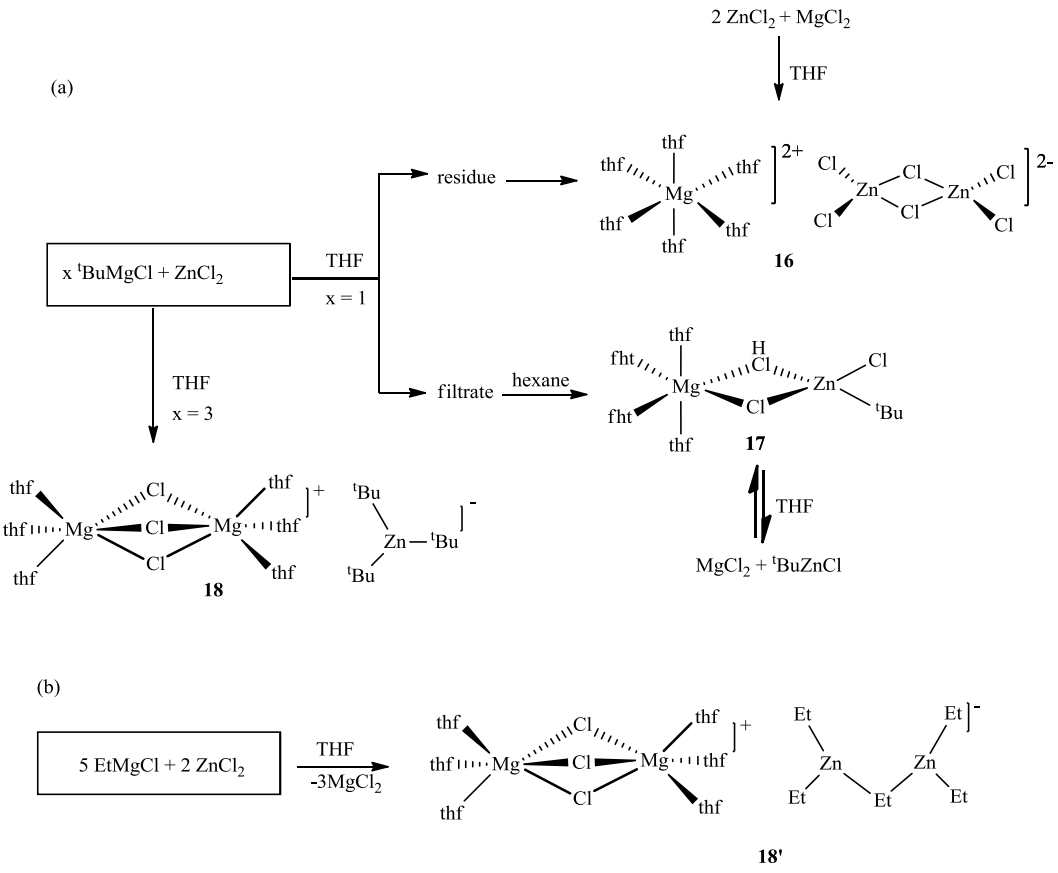
Recently, Hevia and co-workers[52] reported the syntheses and characterization of a new Zn-Mg hybrid complexes resulting from the reaction of $ZnCl_2$ with ^{t}BuMgCl. The reaction of

stoichiometric amounts of $ZnCl_2$ with ^tBuMgCl in THF gave a white solid which was removed by filtration. The X-ray analysis of the white solid was confirmed as $[\{Mg(THF)_6\}^{2+}\{Zn_2Cl_6\}^{2-}]$ (**16**) (**Scheme 1.5a**). Complex **16** exist as solvent-separated ion pairs where the magnesium cation was surrounded by six molecules of THF and formed octahedral geometry while the anionic moiety had two zinc atoms bridged with two chlorine atoms and two terminal chlorines in both side and exhibit distorted tetrahedral geometry. The author claimed that ^tBuMgCl equilibrated with $^tBu_2Mg$ and $MgCl_2$ in their solution and the addition of $ZnCl_2$ favored the Zn-Mg mixed metal species **16** probably due to their low solubility in THF. Their rationalization was supported by the successful syntheses of complex **16** during the reaction of $MgCl_2$ with $ZnCl_2$ (2.0 equivalents). On the other hand, addition of hexane to the first filtrate gave a second solid that was identified as heterobimetallic complex $[(THF)_4Mg(\eta\text{-}Cl)_2Zn(^tBu)(Cl)]$ (**17**) based on ^1H, ^{13}C NMR and X-ray crystallographic studies. The X-ray crystal structure of **17** showed the connection of Zn with Mg via two bridging chlorine atoms and formed a planar $Mg(\eta\text{-}Cl)_2Zn$ four-membered ring. In this structure, the attachment of Cl and terminal *tert*-butyl group to the Zn center gave a distorted tetrahedral geometry while the Mg atom get coordinated with four molecules of THF and gave distorted octahedral geometry. The ^1H NMR of **17** in THF-d_8 showed a singlet at δ 0.99 for the *tert*-butyl group and two multiplates at δ 3.63 and 1.77 for the THF displaced by THF-d_8 with a 1:4 integration ratio for ^{t}Bu:THF identical to that observed in crystal structure. The ^{13}C NMR of **17** showed two peaks at δ 21.9 and 33.6 ppm for quaternary carbon and methyl group respectively which were different than that of organomagnesium compounds (i.e., $^tBu_2Mg$, δ 15.8, 36.0 ppm and ^tBuMgCl, δ 15.6, 35.8 ppm) in the identical deuterated solvent. This result suggested the retention of zincate character of complex **17** in the solution. Alternatively, complex **17** was also synthesized by co-complexation of ^tBuZnCl with $MgCl_2$. Although complex **17** was

insoluble in THF, diethyl ether or toluene at room temperature, the hot solution of complex in THF on cooling gave colorless [{Mg $(THF)_6\}^{2+}\{Zn_2Cl_6\}^{2-}$] (**16**) crystals.

To the contrary, the reaction of $ZnCl_2$ with 3.0 equivalents of ^{t}BuMgCl in THF gave a colorless solution that on cooling also gave crystals which were different than **16** or **17**. These crystals were identified as a mixed-metal magnesium-rich zincate complex $[\{Mg_2Cl_3(THF)_6\}^+\{Zn(^tBu)_3\}^-]$ (**18**) using single crystal X-ray crystallography. In this reaction, not a trace amount of complex **16** was observed confirming the highly favored **18** formation process. The X-ray crystallographic study of complex **18** showed a solvent separated ion pair where the cationic species had two distorted octahedral magnesium atoms bridging with three chlorine atoms between them along with three THF units each coordinated on either side of both magnesium center. The attachment of three *tert*-butyl groups to the Zn atom gave a trigonal planar structure of the anionic moiety. A ^{1}H NMR spectrum of **18** in THF-d_8 showed four distinct resonances for the *tert*-butyl group. The resonance at δ 0.91 ppm was assigned to the major anionic $^tBu_3Zn^-$ species while the other three minor absorptions at δ 0.97, 0.88 and 0.86 ppm were assigned for $^tBu_2Zn$ and ^{t}BuMgCl (2-resonances) respectively. These result confirmed the existence of dynamic equilibrium of complex **18** with $^tBu_2Zn$ and ^{t}BuMgCl in solution. Surprisingly, the equilibrium was sensitive to the concentration of complex **18** in solution as significant dissociation of **18** into $^tBu_2Zn$ and ^{t}BuMgCl was observed in more dilute conditions. Hence, the reaction of complex **18** with organic substrate is a concentration dependent process.

Scheme 1.5 Zincate Species in (a) Stoichiometric and Catalytic Reaction of $ZnCl_2$ with ^tBuMgCl and (b) EtMgCl with $ZnCl_2$.[52,53]



On the other hand, the reaction of EtMgCl (3.0 equiv) with $ZnCl_2$ (1.0 equiv) afforded the solvent separated ion pairs of $[\{Mg_2Cl_3(THF)_6\}^+\{Zn_2Et_5\}^-]$ **18'** crystals (**Scheme 1.5, b**). The structure of newly formed crystal **18'** was established by X-ray crystallography.[53] The newly isolated compounds have dinuclear magnesium based cation similar to structure **18** while the anionic part has two distorted trigonal planer zinc centers where two diethyl zinc moiety bridged with ethyl group affording unusual zinc enrich structure.

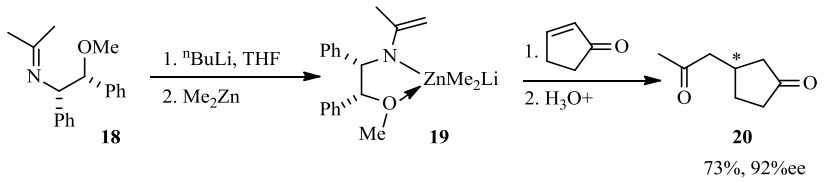
Hence, these results confirmed that the structure of organozincate depends upon the alkyl ligands (e.g., ^{t}Bu vs. Et) employed for the reaction and the actual structure of lithium or magnesium zincates were more complex than that represented by the stoichiometry (i.e., R_3ZnM or R_4ZnM_2). The complex structure of the magnesium-zincate reagents in solution in the presence of stoichiometric or catalytic amounts of zinc (II) salt may reflect the different reactivity of the reagent in organic reactions.

1.6. Types of Reactions

1.61 Organozincates Conjugate Addition Reactions

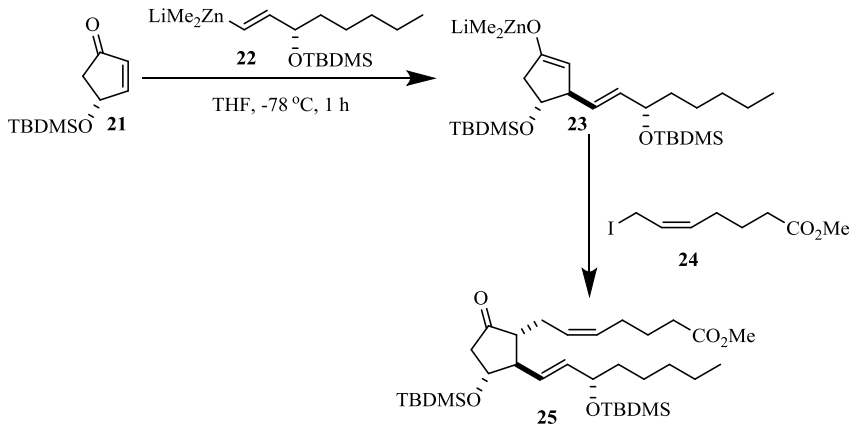
Although both organozincate and organocuprate reagents undergo 1,4-addition to unhindered *α,β*-unsaturated aldehydes, ketones, esters, amides and sulfones, the similarity between these reagents is superficial. The reaction pathways for the 1,4-conjugate addition reactions of these reagents have large differences. A large number of simple or mix organozincate reagents are used for the 1,4-conjugate addition reaction to Michael substrates.[22, 54, 55] Yamamoto and co-workers[54] reported an enantioselective conjugate addition reaction of a chiral mixed organozincate **19**, bearing azaenolate ligands, to the 2-cyclopentenone to afford chiral 3-acetonylcyclopenatnone **20** in good yields and good enantioselectivity (**Scheme 1.6**). Although, the corresponding organocuprate reagents also offer the same products, the yield and enantioselectivity was better with organozincate reagents.

Scheme 1.6 Enantioselective Conjugate Additions of Mixed Organozincates.[54]



A beautiful illustration of the power of organozincate reagents was given in the enantioselective syntheses of prostaglandin derivatives using three component coupling reaction.[55,56] Conjugate addition of lithium (*S*)-3-(*tert*-butyldimethlsiloxy)-1-octenyldimethyl zincate (**22**) to (*R*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopenten-1-one (**21**) give zinc enolate **23** which on coupling with vinyl iodine **24** give chiral prostaglandin derivative **25** in good yield (up to 95%, **Scheme 1.7**). This newly develop method eliminated the necessity of organocopper (I) reagents in the syntheses of prostaglandins as reported by Noyori and Suzuki earlier.[57] Besides, this method displayed high degree of regioselectivity during enolate alkylation and required fewer equivalents of expensive vinyl lithium reagent than the literature example employing divinylcuprate reagents.

Scheme 1.7 Enantioselective Syntheses of Prostaglandin using Organozincate Reagents.[55,56]



Recently, Dieter and Guo[58] reported the conjugate addition of organozincate reagents to *N*-carbamoyl-4-pyridone **26** in the presence of TMSCl to produce 2-substitued 2,3-dihydro-4-pyridone **27** (**Scheme 1.8**). Their results showed that the copper (I) catalyst was not essential for affecting the conjugate addition reaction affording 1,4-adduct in good yields. This method allowed the syntheses of 2-subsituted 2,3-dihydropyridone which was considered as building block for the syntheses of piperidinone, piperidine, indolizidene and quinolizidene alkaloids.

Scheme 1.8 Organozincates 1,4-Conjugate Addition to *N*-Carbamoyl-4-pyridones.[58]

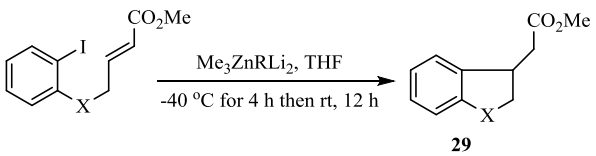
26 **27**

R = Et, 57 %

R = ^{t}Bu, 81 %

Organozincate reagents are also used for the conjugate addition reaction to *α,β*-unsaturated esters.[40,59-61] Uchiyama and coworkers[40] examined the intramolecular Michael addition reactions of organozincate reagents to enoates (**Scheme 1.9**). The author claimed that tetracoordinated zincates, Me_3ZnRLi (R = Me, CN, SCN) undergo iodine-zinc exchange reactions with iodoenoates **28** and form new organozincate reagents that undergo intramolecular conjugate addition to enoate moiety to give bicyclic product **29**. To the contrary, attempted transmetalltion and conjugate addition reaction employing Me_3ZnLi failed under identical reaction conditions.

Scheme 1.9 Intramolecular 1,4-Conjugate Addition of Organozincates to Enoates.[40]



28 X = O, NSO_2Ph

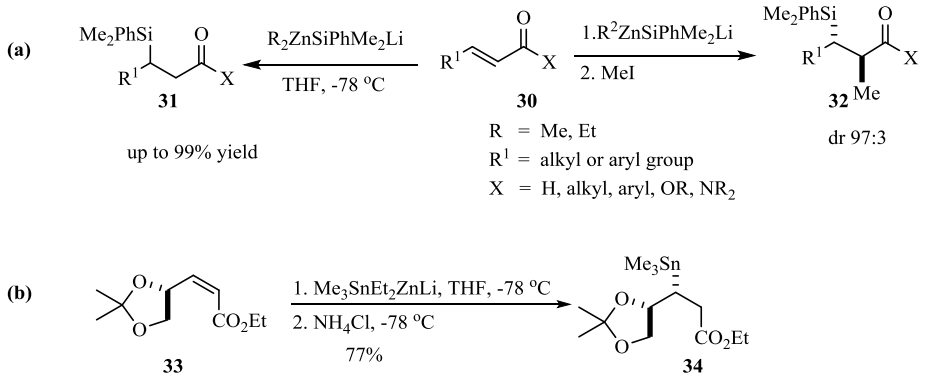
R = Me, CN, SCN

29

up to 66%

Dialkylsilylzincates showed characteristic conjugate addition reaction with less reactive α,β-unsaturated amides and esters derivatives (**Scheme 1.10, a**).[59] The reaction of lithium (phenyldimethylsilyl)dialky1zincate (i.e., $(SiPhMe_2)ZnR_2Li$) with **30** at low temperature gave β-silyl compound **31** in excellent yields. On the other hand, tandem 1,4-conjugate addition reaction of R_2Zn $(SiPhMe_2)Li$ with **31** followed by electrophile trapping gave *anti* α,β-disubstituted product **32** in high stereoselectivity. Although corresponding silyl cuprates also furnished the same product, the yield was better while employing the silylzincate reagents. Krief and co-workers reported the stereoselective conjugate addition reaction of stanyl zincates to enoate during the syntheses of optically active (*1R*)- enantiomer of *trans*-methyl chrysanthemate (**Scheme 1.10, b**).[60] Surprisingly, the stanyl zincates underwent conjugate addition to the enoates from the face opposite than that of organostanyl lithium reagents and maintained the required stereochemistry. This result confirmed the effect of counter ion in the conjugate addition reaction. Although stanyl cuprates also offered similar results, the best diastereoselection was observed with zincate reagents.

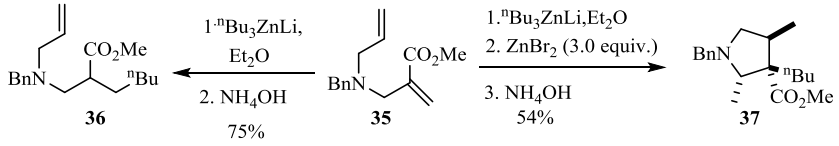
Scheme 1.10 Conjugate Addition of Silyl- and Stanylzincates to Michael Acceptors.[59,60]



Organozincate reagents can also undergo Michael Initiated Ring Closure (MIRC) reaction with *N*-allyl substituted enoates **35** in the presence of excess amounts of Zn (II) salts

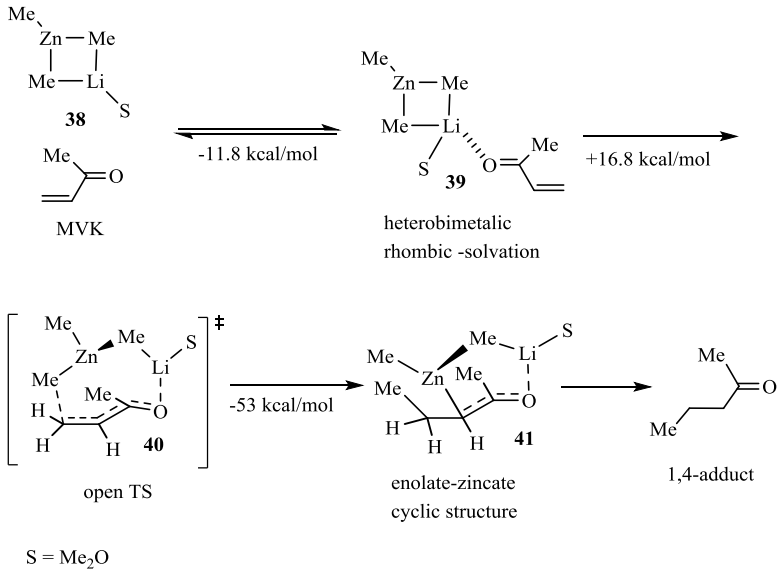
(**Scheme 1.11**). Although, the reaction of lithium tributylzincate with enoate **35** gave good yield of 1,4-adduct **36** in Et_2O, the addition of excess amounts of zinc bromide in the reaction medium gave the cyclopentyl derivatives in moderate yield but with good diastereoselectivity.

Scheme 1.11 Additions of Lithium Tributylzincates to Conjugated Ester.[61]



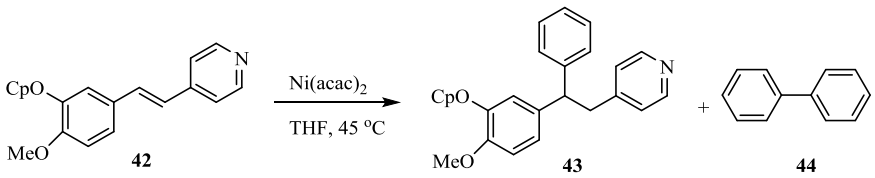
Nakamura and coworkers[27] investigated the pathway for the conjugate addition reaction of organozincate reagents to Michael substrate such as *s-trans* methyl vinyl ketone (MVK) using theoretical/computational model (i.e., Density Functional Theory (DFT) calculations) for understanding the mechanism of ligand transfer in the reaction. The initial step of the pathway involves equilibrium between rhombic bimetallic zincate (**38**) and MVK with their association complex **39**. The formation of the association complex elongates the C-Li-C bond length of **38**. The cleavage of one of the Me-Li electrostatic bond of rhombic bimetallic structure **38** followed by interaction of the methyl group with the π^* orbital of the carbon-carbon double bond of MVK results subsequent shorting of the distances between β-carbon atom of MVK with the Me group and gave open transition state **40**. The formation of the transition state **39** was an endothermic process (16.8 kcal/mol). Finally, the complete transfer of the methyl group through the central Zn atom to MVK gave the zincate-enolate cyclic structure **41** with the release of huge amounts of energy (-53.0 kcal/mol). The author claimed that the 1,2-addition reaction was energetically less favorable than 1,4-additions based on their energy calculations. Hence, 1,4-conjugate addition of organozincates took place via open transition state without any reduction/oxidation on Zn and Li centers.

Scheme 1.12 Conjugate Addition of Lithium Trimethylzincate to Methylvinylketone.[27]



Although not common, nickel (II) salts can catalyze the conjugate addition of organozincate reagents to activated unsaturated compounds. The reaction is synthetically interesting due to the involvement of unique Ni^{I}/Ni^{II} oxidation state or more common Ni^{0}/Ni^{II} oxidation state in the course of the catalytic cycle. Houpis and co-worker's reported the nickel acetylacetonate [$Ni(acac)_2$] catalyzed conjugate addition reaction of alkyl/aryl zincates to 4-substitued vinyl sulfoxide affording moderate to good yields of triaryl-ethyl derivatives. The protocol can also be used for the highly difficult conjugate addition reaction to vinyl pyridine **42** with good yields of triaryl-ethyl derivatives **43** (**Scheme 1.13**).[62] One of the major limitations of the process was the formation of biphenyl while employing expensive aryl groups for the reactions. This problem can be minimized by using mixed organozincates bearing only one aryl group. The triaryl-ethyl derivatives (i.e., **43**) are used as phosphodiester IV (PDE-IV) inhibitors for the treatment of dementia, depression, coronary heart disease, pulmonary arterial hypertension, and schizophrenia.

Scheme 1.13 $Ni(acac)_2$ Catalyzed Addition of Arylzincates to Vinyl Pyridine.[62]



42 **43** **44**

Cp = Cyclopentyl

2 equiv. $Ph_3ZnMgCl$	93%	50%
2 equiv. Ph_3ZnLi	67%	50%
1.2 equiv. $PhZnMe_2MgCl$	65%	3%

1.62 Organocopper Conjugate Addition Reactions

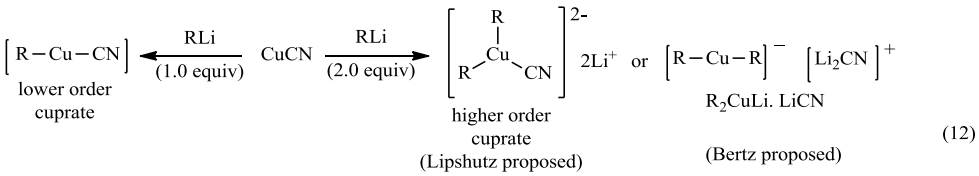
Organometallic reagents hold great promises for the construction of carbon-carbon bond during the syntheses of complex organic molecules from simple ones. Among them, organocopper reagents are one of the most reliable organometallic reagents for the successful construction of carbon-carbon bond in sp, sp^2 and sp^3 carbon centers. After the first preparation of phenyl copper by Reich[63] in 1923 and later Gilmann's[64] subsequent report for the syntheses of lithium dimethylcuprate, organocuprate reagents are increasingly used for conjugate addition to *α,β*-unsaturated aldehydes, ketones, esters, acids, nitriles and amides.[6] Like lithium trialkylzincates, lithium dialkylcuprates are more reactive than the corresponding monoalkyl copper reagents. Although, both organozincates and organocuprates derived from the corresponding organolithium or organomagnesium reagents have been used for the conjugate addition reactions, the reactivity and mechanistic profiles of these reagents are completely different. The high reactivity of organocuprates towards Michael substrates can be rationalized in terms of the presence of high lying copper 3d orbitals, that can mix with the alkyl group "s" and "p" orbitals. In contrast to the organocopper chemistry where the oxidation/reduction of Cu(I)/Cu(III), Cu(I)/Cu(II) and vice

versa are the common process, organozincates lack such higher oxidation states [Zn (IV)] and hence behaved differently during the reaction. Previously, our group reported several research articles[58,65-68] utilizing organocopper (RCu), organocuprate (R_2CuLi), heteroleptic organocuprates RCu(X)Li, *α*-amino and *α*-(*N*-carbamoyl)alkylcuprates in the conjugate addition reaction.

Monoalkyl copper and dialkyl cuprate are generally prepared by the reaction of a copper (I) salt [e.g., CuCN, CuX (X= Cl, Br, I)] with alkyl lithium,[69] Grignard reagents,[70] organozinc,[71] organoaluminium,[72] or organostannane[73] reagents. Depending upon the nature of the counter ions, stoichiometry of the copper salts, and types of solvents, the reactive species will be varied.

$$CuX \xrightarrow[X = CN, \text{ halides}]{2RLi} R_2CuLi + LiX$$

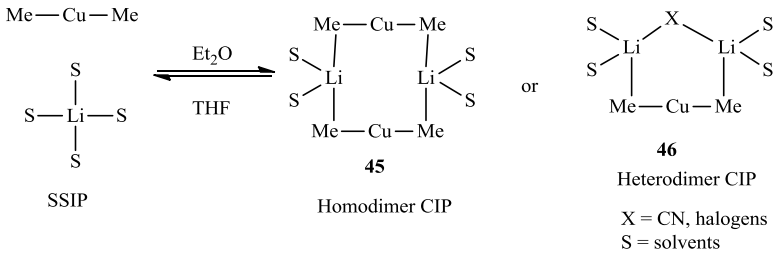
Copper cyanide (CuCN) is a commonly used copper (I) salt for the preparation of copper reagents because of its stability towards air and ease of purification. When one equivalent of organolithium is treated with CuCN, an alkyl/arylcyanocuprate is formed where the alkyl/aryl group can act as a transferring ligand and cyanide anion as a non-transferring ligand. Two equivalents of organolithium reagents with CuCN give "cyano-Gilmann reagent" [i.e., $R_2CuLi.LiCN$]. Lipsutz claimed that cyano-Gilman reagents are higher order cuprates as the ratio of Li/Cu > 1. Although, there was a big controversy about the structure of cyano-Gilman reagents whether both the organic group and cyano group are attached to copper as proposed by Lipsutz[74] or the cyano group is attached to lithium as proposed by Bertz, the Bertz proposal was accepted based on evidence accumulated from X-ray absorption near edge structure (XANES),[75] IR absorption (CN),[76] NMR spectroscopy[77] and theoretical calculations.[78]



(12)

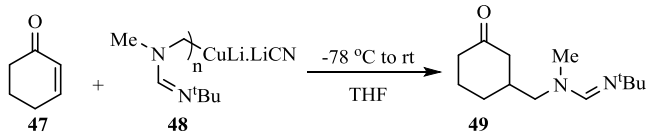
In order to understand the mechanism and reactivity of organocuprate reactions, it's noteworthy to characterize the reacting species under different conditions. In the last three decades, a vast amount of research has been carried out for determining the structure of organocuprates. A structural analysis by Pearson and coworkers[79] using ^{1}H-NMR studies, vapor pressure depression, and solution X-ray scattering methods showed that lithium diorganocuprate existed as contact ion pairs (CIPs) in homo-dimer **45** or hetero-dimer **46** form in poor lithium salt coordinating solvents like diethyl ether (**Scheme 1.14**). On the other hand, solvent separated ion pairs (SSIPs) were reported as an exclusive species in good lithium salt-coordinating solvents like THF, DME or crown ethers. These results are further supported by Gschwind and coworkers[80] investigations where homodimeric core structure of $Me_2CuCN{\cdot}LiCN$ in Et_2O was established using ^{1}H, ^{6}Li HOE and ^{1}H, ^{1}H NOE NMR studies. Currently numerous research articles, over twenty review articles[81] and a few book chapters[6, 82,83] exist in the literature emphasizing the use and structural identification of organocuprate reagents in solution and solid states.

Scheme 1.14 Structure of Lithium Dimethylcuprate in THF and Et_2O.[79]



Alkyl, aryl, *α*-amino and *α*-(*N*-carbamoyl)alkylcuprates undergo conjugate addition reaction to large numbers of Michael acceptors including acyclic and cyclic enones and enals, *α,β*-alkenyl, *α,β*-alkynyl, *α,β-β,γ*-allenyl, *α,β,γ,δ*-dienylcarboxylic acid, nitriles and sulfoxides as demonstrated by several groups earlier and later by Dieter's and coworkers.[67,68] *α*-Aminoalkyl(cyano)cuprates (**48**) prepared from *tert*-butylformamidine also undergo 1,4-conjugate addition to 2-cyclohexenone (**47**) at lower temperature (**Scheme 1.15**).

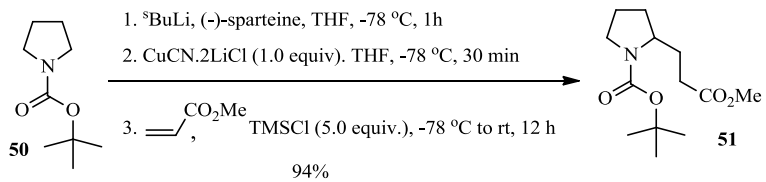
Scheme 1.15 1,4-Addition of *α*-Aminoalkyl(cyano)cuprate to 2-Cyclohexenone.[67]



47 **48** **49**

The conjugate addition reaction of organocuprate reagents to *α,β*-enoates proceeds only in the presence of $BF_3{\cdot}OEt_2$[84] or chlorotrimethylsilane (TMSCl).[68] The reaction of *α*-(*N*-carbamoyl)alkylcuprate with methyl crotonate failed in the absence of additives but successfully completed in the presence of TMSCl (5.0 equiv) under identical reaction conditions with excellent yields (**Scheme 1.16**). This reaction was successfully extended for the 1,4-conjugate addition to *α,β*-unsaturated thiol esters, imides, nitriles, alkynyl esters, sulfoxides and with *α,β-γ,δ*-unsaturated allenyl esters with poor to excellent yields and stereoselectivity depending upon the electron-withdrawing substituent and the substitution pattern of the unsaturated substrate.

Scheme 1.16 Conjugate Addition of *α*-(*N*-carbamoyl)alkylcuprates to Enoates.[68]

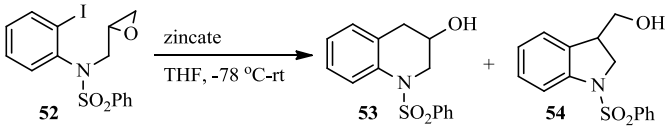


50 **51**

1.63 Epoxide Opening Reactions

Epoxides (oxiranes) are three member cyclic ethers that have high ring strain and hence undergo ring opening reactions with varieties of organometallic (e.g., organolithium, organomagnesium, organocuprate, organozincate and organoaluminate) reagents. Controlling the regioselectivity in the reaction of organometallic reagents with vinyl epoxides usually suffer problems due to the competitive S_N2 and S_N2' epoxide opening reactions. The regioselectivity of the epoxide opening (i.e. S_N2 or S_N2') pathway however depends upon organometallic reagents used for the reaction. Uchiyama and co-workers[40] reported a regioselective S_N2 opening of epoxide **52** with organozincate reagents affording moderate to good yields of 6-*endo*-cylization (**53**) or 5-*exo*-cyclization (**54**) products (**Scheme 1.17**). The intramolecular S_N2 opening reaction of epoxides with zincate reagents gave the mixture of *endo*- and *exo*- cyclization product. Interestingly, application of Me_3ZnLi for the reaction with **52** predominantly gave an *anti*-Baldwin's rule product (i.e., the *endo*-cyclized 1,2,3,4-tetrahydroquinoline derivatives **53**). To the contrary, application of highly coordinated zincates Me_3ZnRM_2 (R= Me, SCN) gave a major Baldwin's rule product (i.e., an exo-cyclized indoline derivatives **54**). The method could be used for the asymmetric syntheses of 3-hydroxytetrahydrooquinoline and 3-indolinemethanol, an active constituent of antitumor derivatives such as CC-1065[85] and duocarmycin[86] pharmacophores. Although, the detailed structural analysis of the Me_3ZnRM_2 zincates is yet to be established, the tetracoordinated dianionic zinc structure of $Me_3ZnCNLi_2$ where CN get directly attached to Zn atom was established by EXAFS spectroscopy and further supported by ^{1}HNMR/Raman/in situ FTIR and DFT calculations. This structural rationale also supported the experimental results where tetracooridnated zincates have higher reactivity and different chemoselectivity compared to trialkylzincates.

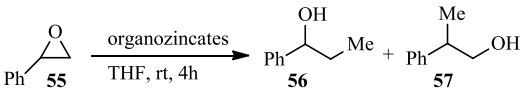
Scheme 1.17 Intramolecular Epoxide Opening with Organozincate Reagents.[40]



zincate	% yield (**53**+**54**)	**53**:**54**
Me_3ZnLi	86	96:4
Me_4ZnLi_2	67	13:87
$Me_3Zn(SCN)Li_2$	92	3:97

On the other hand, application of trialkyl or tetracoordinated organozincates for the reactions with styrene oxide gave the mixture of 1-phenyl-1-propanol (**56**) and 2-phenyl-1-propanol (**57**) with none to small regioselectivity (**Scheme 1.18**). The reaction of Me_3ZnLi with **55** gave slightly higher amounts of **56** while application of $Me_3Zn(CN)Li_2$ under identical condition gave **57** as a major product. The low regioselectivity in the reaction was rationalized due to the unsymmetrical nature of epoxide employed for the reactions.

Scheme 1.18 Intermolecular Epoxide Openings with Organozincate Reagents.[40]

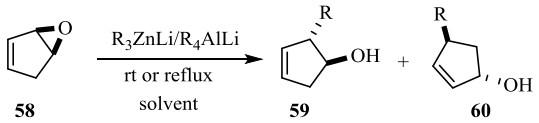


zincate	**56**:**57**	% yield (**56**+**57**)
Me_3ZnLi	56:44	70
Me_4ZnLi_2	51:49	93
$Me_3Zn(CN)Li_2$	29:71	41

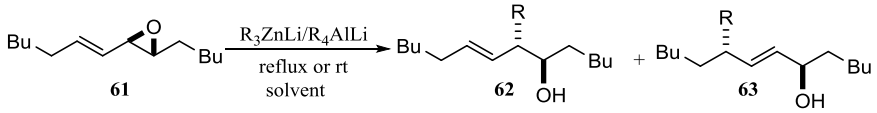
The nucleophilic addition of organometallic reagents to vinyl epoxides usually proceeds via S_N2 or S_N2' pathway depending upon nature the reagents used for the reaction. Organocuprate or copper catalyze reactions of organolithium, organomagnesium or organozinc reagents with vinyl epoxides preferably undergo S_N2' epoxide opening pathway.[87] However, organozincate and

organoaluminate reagents preferred regioselective S_N2 *anti* opening reactions with cyclic and acyclic non functionalized epoxides (**Scheme 1.19**).[20] Although solvent has little influences on regioselectivity, more S_N2' opening product was observed in non-coordinating solvent (hexane). The authors claimed that the organozincate reagents exist as contact ion pairs in non-coordinating solvents where the coordination of lithium organozincates with epoxide activated the carbon bearing epoxide and terminal carbon atom of the double bond. On the other hand, organozincate reagents exist as solvent separated ion pairs in THF hence coordination between oxygen and organometallic reagents cannot formed. This difference in complex formation in coordinating or non-coordinating solvents gave slight differences in regioselectivity of the process.

Scheme 1.19 Regioselective Reactions of Organozincates and Organoaluminates with Cyclic and Acyclic Epoxides.[20]



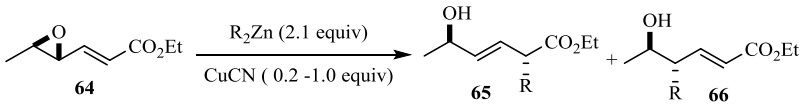
Zincate/Aluminates	Solvent	**59:60**	% Yield (**59+60**)
Bu_3ZnLi	THF	100:0	75
Bu_3ZnLi	hexane	84:16	68
Me_3ZnLi	THF	100:0	33
Me_3ZnLi	hexane	83:17	34
Bu_4AlLi	hexane	92:8	89
Me_4AlLi	hexane	95:5	18



Zincate/Aluminates	Solvent	**62:63**	% Yield (**62+63**)
Bu_3ZnLi	THF	87:13	43
Bu_3ZnLi	hexane	73:27	77
Me_3ZnLi	THF	79:21	84
Bu_4AlLi	Et_2O	91:9	75
Bu_4AlLi	hexane	41:59	83

Similar to non-functionalized vinyl epoxides, organocuprate or copper catalyzed reaction of Grignard or organozinc reagents to the functionalized vinyl epoxides proceed via S_N2' pathway.[66,88] Recently, organocuprate or copper catalyzed reaction of Grignard or organozinc reagents to vinyl epoxides containing conjugated carboalkoxy functionality or protected alcohol functionality was examined in our group with an aim of generating vicinal stereogenic centers via bis tandem allylic substitution reactions (**Scheme 1.20**).[88] The reaction of dialkyl zinc with ethyl *γ,δ*-epoxy-*α,β*-hexenoate (**64**) in the presence of catalytic amounts of Cu(I) salts gave preferential S_N2'-allylic substitution product in good to excellent yields with excellent *anti* selectivity. The use of salt free (i.e., LiX) dialkylzinc and CuCN in THF or DMF with epoxyenoate **64** gave optimal 1,4-regioselectivity with *anti*-diastereoselectivity.

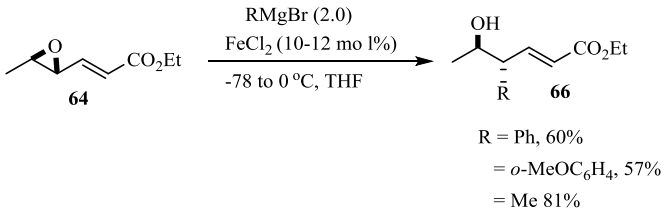
Scheme 1.20 Copper Catalyzed S_N2'-Allylic Substitution on **64**.[88]



R = Et, ^{n}Bu , 73-90 %
S_N2':S_N2 76:24-94:6, anti:syn 94:6-98:2

On the other hand, organoiron reagents prefer S_N2 epoxide opening reactions with functionalized allyl epoxide. The reaction of Grignard reagents with epoxyenoate **64** in the presence of catalytic amounts of iron (II) chloride gave exclusive S_N2-epoxide opening products with good to excellent yield.[89] The author claimed that the reaction was preceded via π-allyliron intermediate with exclusive formation of *anti* substitution products.

Scheme 1.21 $FeCl_2$ Catalyzed Reactions of Grignard Reagent with **64**.[89]

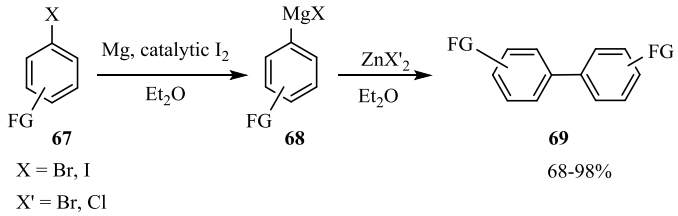


These literature results confirmed that the choice of organometallic reagents and catalytic systems were crucial for controlling the regioselective opening of epoxide. During our research, we sought to investigate the regioselective S_N2 openings of epoxyenoate **64** using organozincate reagents using the conditions previously established by Alexakis and co-workers for regioselective opening of cyclic and acyclic non-functionalized epoxides (*vide supra*).[20] Although, the S_N2 epoxide opening of **64** employing organoiron reagents was reported before we published our results, the continued investigation on organozincates chemistry was directed for developing alternative methodology leading to S_N2 epoxide opening product. Surprisingly, our investigation uncovered the novel feature of organozincate chemistry where organozincate reagents underwent exclusive Michael Initiated Ring Closure (MIRC) reactions with epoxyenoate **64** and gave cyclopropane derivatives with excellent yields and excellent diastereoselectivity. These results will be discussed thoroughly in chapter 2 of this dissertation (*vide infra*).

1.64 Cross-coupling Reactions

The homocoupling reaction of arylzincates in the presence of nickel salt was previously described.[62] Arylzincate reagents showed their versatility in Negishi coupling,[11,12] Fukuyama coupling,[13] and oxidative coupling reactions.[14,15] Palladium catalyzed cross coupling reaction of functionalized organozincate reagents with heteroarylhalide is an efficient method for the syntheses of unsymmetrical coupling products.[25,90] Currently, several aryl-metal reagents based on Co(II), Cu(II), Ti(IV) or V(V) have been employed for the homo-coupling reactions. Zinc halide ($ZnBr_2$ and $ZnCl_2$) catalyzed oxidative homo-coupling reaction of several aryl Grignard reagent in the presence or absence of oxidant (i.e., dibromoethane) was also reported in the literature (**Scheme 1.22**). These reactions gave symmetrical biphenyl compounds in excellent yields in short time.[91]

Scheme 1.22 Homo-Coupling Reaction of Aryl Grignard Reagent.[91]



67 **68** **69**

X = Br, I

X' = Br, Cl

68-98%

Our investigation in organozincate chemistry also supported the literature results where aryl lithium/magnesium reagents underwent self-coupling reaction when catalytic or stoichiometric amounts of zinc salts were employed for the reaction. This result will be discussed thoroughly in chapter 2.

1.7 Conclusion

Carbon-carbon bond formation reaction employing organometallic reagents in regio- and stereo controlled fashion is a central challenge in synthetic organic chemistry. Among the various kinds of organometallic reagents used for the reaction, the unique reactivity/selectivity pattern of the organozincate reagents with different substrates allured the attention of synthetic organic chemist for the construction of C-C bond in recent years. An important advantage of the use of organozincate reagents has the possibility of transferring functionalized ligand during the reaction. A beautiful examples for these reactions involved the reaction of functionalized organozincate reagents for the epoxide openings,[20] 1,2-addition to carbonyl,[21] 1,4-conjugate addition to the Michael substate,[22] benzyne formation,[23] *ortho*-metallation,[24] cross coupling,[25] and anionic polymerizations[26] reactions. The versatility of organozincate reagents will be discussed in chapter 2 and chapter 5 of this dissertation. For example, the application of organozincate reagents in the MIRC reactions of epoxyenoate, epoxyenone, epoxyensulfone and epoxyenamide for the diastereoselective syntheses of cyclopropane derivatives will be discussed in chapter 2 while chapter 5 will focus on the regioselective 1,4-conjugate addition reactions of organozincate reagents to nitrodiene, thiodieonate and ketodiene.

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CHAPTER II

REGIO- AND STEREOCONTROLLED CONJUGATE ADDITION-MICHAEL INITIATED RING CLOSURE (MIRC) REACTIONS

2.1. Introduction

The discovery and development of new synthetic methods hold great promise and continue to be important arenas in organic synthesis.[1] Reactions that involve the formation of multiple bonds, rings and stereo centers are particularly important for the efficient synthesis of complex molecular structure.[2] Among the various types of reactions studied, conjugate addition reactions of organometallic reagents to Michael substrates has been vastly elaborated in recent years because of their broad synthetic utility for the synthesis of natural and non-natural products. Organometallic reagents such as organolithium, Grignard and their corresponding cuprate, zincate, or aluminate reagents undergo conjugate addition to Michael substrates (e.g., α,β-unsaturated esters, aldehydes, ketones, sulfones, amides, nitriles, nitrites and phosphates) in the presence or absence of *trans*ition metal catalysts.[3] These reactions demonstrate the synthetic utility of organometallic reagents in carbon-carbon bond formation and significantly broaden the scope of conjugate addition reactions.

The synthesis of cyclopropane derivatives has attracted significant interest of organic chemist as these compounds are structural subunits over 4000 biologically active natural products [e.g., pheromones, terpenes, amino acids, and fatty acid metabolites] and over 100 pharmacological products.[4] The presence of three tetravalent carbons in the cyclic structure of cyclopropane produces high ring strain in the molecules. However, the highly strained nature of cyclopropane is

boon to the synthetic chemist as these molecules have tunable reactivities and can therefore be used as synthetic precursors for the synthesis of functionalized and non-functionalized complex organic molecules by performing cyclopropane ring opening reactions.[5, 6,7]

2.2 Synthesis of Cyclopropane Derivatives

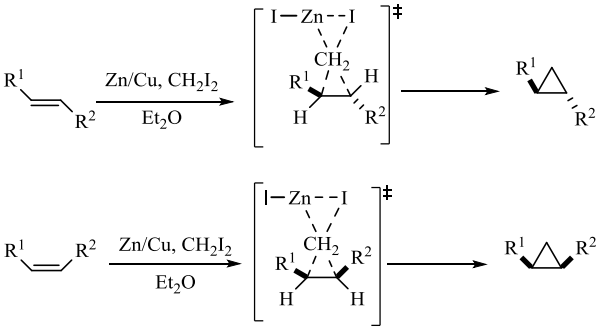
Considerable effort has focused toward the development of new methodologies for the regio- and stereoselective synthesis of cyclopropane derivatives in recent years. The usefulness of these synthetic protocols becomes more apparent once the biological activity of the compounds was explored. One of the most appealing strategies for the synthesis of cyclopropane derivatives is a concerted addition of methylene group to the alkene while few other strategies for cyclopropantions are abundantly reported in the literature. Among them, the most commonly used methods include;

2.21 Simmons-Smith Cyclopropanation Reaction

Simmons-Smith cyclopropanation reaction is one of the most widely used methods for the stereospecific synthesis of cyclopropane derivatives present in several natural products and synthetic intermediates and usually proceeds via carbenoid intermediate. This reaction was first reported by Simmons and Smith during the reaction of diiodomethane with cyclohexene in the presence of zinc-copper couple affording bicyclic [4.1.0] heptanes in moderate yields (48%).[8] The versatility of the reaction was confirmed by their successful implementation for the cyclopropanation reaction of non-functionalized and functionalized alkenes such as ethylene, cyclopentene, bicycle [2.2.l] hept-2-ene, 3-phenyl-propene, styrene, 1-(*o*-methoxyphenyl)-propene, methyl crotonate and vinyl acetate with diiodomethane in the presence of Zn-Cu couple.[8] Besides, this method was compatible with alkenes bearing several functional groups

including esters, ketones, enol ethers, enamines. One of the most challenging issues of the methodology includes the difficulties for controlling the stereochemistry of cyclopropanation reaction in multi-unsaturated alkenes where cyclopropanation usually preced in less hindered double bond. In addition, the presence of hydroxyl group adjacent to double bond usually directs the *cis*-cyclopropanation reaction on coordination with Zn or Cu carbenoids. Currently, several metallating reagents including $ISmCH_2I$, $EtZnCH_2I$, $CF_3COOZnCH_2I$, R_2AlCH_2I are used for the synthesis of cyclopropanation products employing Simmons-Smith reactions.[9]

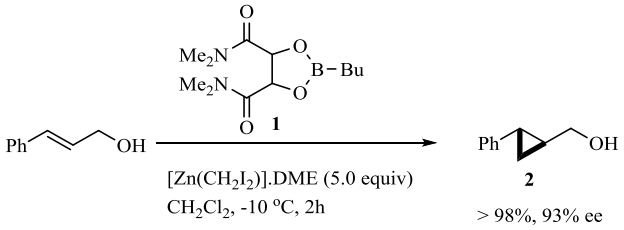
Scheme 2.1 Simmons-Smith Cyclopropanation Reactions.[9]



The last two decade witnessed a dramatic upsurge in methodologies for the enantioselective Simmons-Smith cyclopropanation reaction of alkenes using chiral catalyst. Independent study by Furukawa groups[10] and Inouye groups[11, 12] on enantioselective Simmons-Smith reactions of alkenes in the presence of stoichiometric amounts of L-leucine and (-)-menthol respectively failed to induce desired sterechemistry. Kobayashi and coworkers reported a major breakthrough in the enantioselective Simmon-Smith cyclopropanation of alkene using procedure catalytic in C_2-symmetric chiral disulfonamide.[13-15] Thereafter, Charente and co-workers[9, 16, 17] further extended the field by exploring the enantioselective cyclopropanation reaction of cinnamoyl alcohol (**7**) with excess amounts of [$Zn(CH_2I_2)$].DME (1,2-dimethoxyethane, 5.0

equiv) in the presence of catalytic amounts of chiral dioxaborolane **1**. This reaction gave *trans*-cyclopropane product **2** in excellent yield with good enantioselectivity (**Scheme 2.2,** up to 98%, 93% ee).

Scheme 2.2 Enantioselective Cyclopropanation Reaction of Cinnamoyl Alcohol.[16]

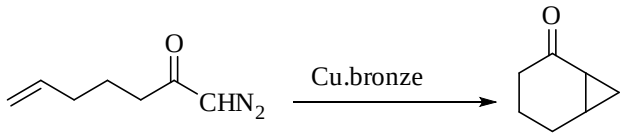


2.22 Transition Metal Catalyzed Decomposition of Diazo Compounds

Another efficient method for the cyclopropanation reactions is the generation of carbene species in the decomposition reaction of diazocompound with catalytic amounts of transition metals followed by their in situ trapping with alkenes. The most effective transition metal catalysts used for these reactions are copper and rhodium based complexes but several other transition metals such as cobalt, nickel, iron, molybdenum, zinc, palladium, ruthenium, renium and tungeston complexes also promoted the decomposition of diazoalkanes and generate carbene that undergo concerted cyclization reaction with alkene to give cyclopropane derivatives.[18] Generally, the nature of diazocompounds and the type of reactions (e.g.; intra- vs intermolecular) play a crucial role for the employment of transition metal catalyst used for the reaction. The intramolecular cyclopropanation reaction involving unsaturated diazo-substrate was first reported by Stork and Ficini[19] in 1961 during the copper bronze catalyzed decomposition of 5-hexenoic diazoketone followed by trapping of in-situ generated carbene to form [4,1,0] bicyclohepta-2-one. Since then,

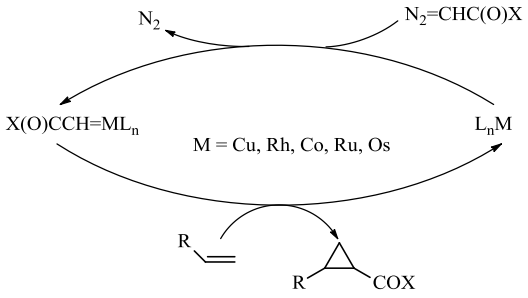
several examples on intramolecular and intermolecular cyclopropanation reactions involving diazo substrates are explored.[9, 20]

Scheme 2.3 Intramolecular Cyclopropanation of 5-Hexenoic Diazomethylketone.[19]



In intermolecular cyclopropanation reaction, a carbene intermediate generated during the transition metal catalyzed decomposition of azocompound is trapped by second olefin molecules to give cyclopropane derivatives. Diazomethane (CH_2N_2) is the simplest diazoalkane used for the intermolecular cyclopropanation reactions. Some other azo compounds like trimethylsilanediazomethane ($TMSCHN_2$), phenyldiazomethane ($PhCHN_2$), ethyl diazoacetate ($EtOOCCHN_2$), 2,6-di-*tert*-butyl-4-methylphenyldiazoacetate ($BHTOOCCHN_2$, BHT = 2,6-di-*tert*-butyl-4-methylphenyl), diazophosphates ($N_2CHPO(OR)_2$ (R = Me, Et, ^{i}Pr)), cyanodiazomethane (N_2CHCN), sulfonyl diazometane (N_2CHSO_2R), nitro diazomethane (N_2CHNO_2), dimethyl diazomalonate ($N_2C(COOMe)_2$), and *tert*-butyl-α-nitro diazoacetate ($N_2C(NO_2)COO^{t}Bu$) are also abundantly used for the cyclopropanation reactions.[9, 21]

Scheme 2.4 Catalytic Cycle for Metal Catalyzed Cyclopropanation Reaction.[9]

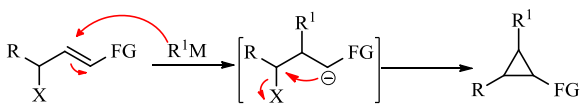


The employment of potentially hazardous diazocompounds[22] and the formation of alkene as byproducts of the reaction due to the coupling of in situ generated carbenes in most of the transition metal catalyzed reactions limit their synthetic utility.

2.23 Michel Initiated Ring Closure (MIRC) Reaction

Although the chemistry of *Michael Initiated Ring Closure* (MIRC) reaction is not as pervasive as the Simons-Smith cyclopropanation or *trans*ition metal catalyzed decomposition of diazocompounds followed by trapping of in situ generated carbene, the opportunity of using carbon, heteroatom nucleophiles and organometallic reagents in the MIRC reaction attracted the increased attention of synthetic organic chemist in these reactions. The MIRC reaction was first discovered by Little and Dawson[23] in the reaction of haloenoate with nitrogen and sulfur nucleophiles during the synthesis of disubstituted cyclopropane, cyclopentane, cyclohexane and cycloheptane derivatives (*vide infra*). In these reactions, nucleophilic reagents undergo conjugate addition to the Michael substrates and form stabilized anions which in turn undergo in situ ring closure reaction to give cycloalkane derivatives (**Scheme 2.5**). Cyclopropanation reactions involving MIRC pathway are non stereospecific as both *trans*- and *cis*-alkenes give the *trans* products. However, stereospecificity can be achieved when the ring closure occurs faster than rotation around the carbon-carbon single bond once conjugate addition preceed.

Scheme 2.5 Cyclopropanation Reaction via MIRC Pathway.



FG = Funtional group
X = Leaving group

Depending upon the leaving group present in the substrate or in the nucleophile, MIRC reactions are categorized into two types.

2.23.1 MIRC Reactions Bearing a Leaving Group in the Substrate

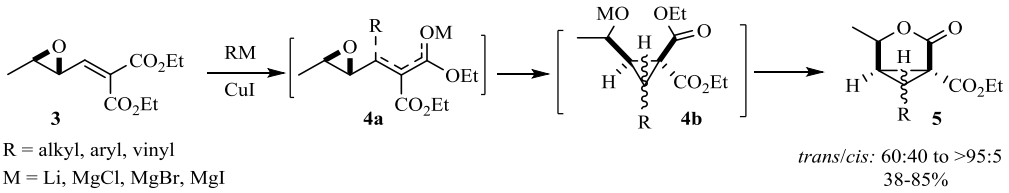
Michael acceptors bearing a leaving group in the γ-position are prone to undergo MIRC reactions with nucleophilic reagents. Currently, the practical applicability of the MIRC reactions bearing the leaving group in the substrate are largely limited to substrates like phenyl vinyl epoxides,[24] epoxy vinyl esters,[25] aziridinyl vinyl esters,[26] and α,β-unsaturated-γ-haloesters.[27]

2.23.11 Oxygen or Nitrogen as Leaving Group

Vinyl epoxides and vinyl aziridines are highly attractive synthons in organic chemistry. Vinyl epoxides usually prefer to undergo regioselective S_N2-epoxide opening reactions with hard nucleophiles like organolithium,[24, 25, 28-30] Grignard,[31, 32] organoiron,[33] organozincate,[34] and organoaluminate[34] reagents while soft nucleophiles like organocopper,[35-37] copper catalyzed organolithium and Grignard reagents,[38, 39] prefer S_N2'-epoxide opening pathway.

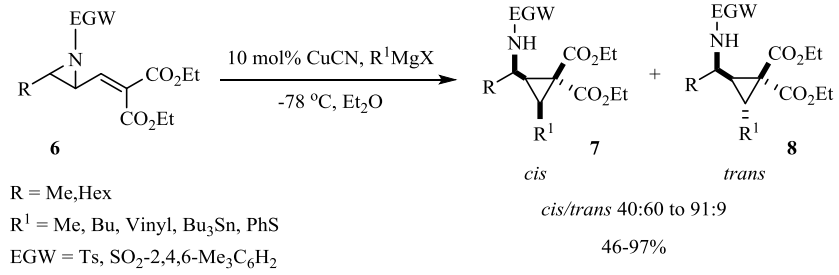
Kasatkin and co-workers[36] reported that organolithium or Grignard reagents undergo conjugate addition reaction to doubly activated epoxy substrate such as diethyl γ,δ-epoxy-α,β-unsaturated butylidene malonate (**3**) in the presence of catalytic amounts of copper(I) salt (**Scheme 2.6**). The conjugate addition of organocuprate reagents to Michael substrate give stabilized enolate **4a** that undergo in situ cyclization to form cyclopropane derivatives **4b**. The second cyclization of **4b** gave bicyclic lactone **5** with in moderate to good yields (38-85%) and poor to good diastereoselectivities (*trans:cis*; 60:40-<95:5). However, attempted reaction of these reagents with mono activated substrate (i.e., ethyl γ,δ-epoxy-α,β-unsaturated hexenoate) failed under identical reaction conditions.

Scheme 2.6 Diastereoselective Cyclopropanation Reaction of Epoxymalonate **3**.[36]



Funaki[26] reported an analogous copper catalyzed conjugate addition reaction of Grignard reagents to diethyl aziridinylmethylenemalonate **6** (**Scheme 2.7**). A variety of Grignard reagents (i.e., alkyl, vinyl, tributylstannyl or thiophenyl) undergo MIRC reactions with **6** affording 1,1,2,3-tetrasubstituted cyclopropane derivatives **7** and **8** in moderate to good yields (46-97%) and poor to good diastereoselectivities (*E*/*Z* 60:40-9:91). Contrary to Kasatskin model, *cis*-cyclopropyl derivative was observed as major product in the reaction.

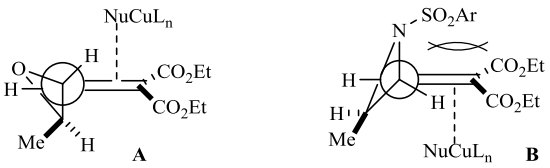
Scheme 2.7 Diastereoselective Cyclopropanation of Aziridinyl Malonate.[26]



This opposite diastereoselectivity of the cyclopropanation product observed in the copper catalyzed reaction of Grignard reagents with epoxymalonate **3** and aziridinyl-methylenemalonate **6** was rationalized by Yamamoto model (**Scheme 2.8**).[40] According to this model, conjugate addition of organocuprate reagents to a Michael substrate can be governed by steric factors rather than stereo-electronic ones. The high electron donating ability of organocuprate reagents

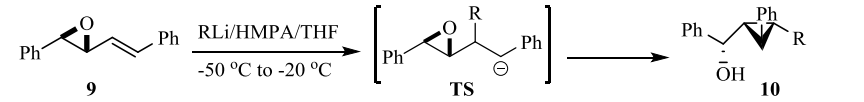
preferred attack to the epoxymalonate **3** in the most stable conformation (i.e., the carbon-carbon bond of the epoxide is perpendicular to the alkene C=C). The attack of organocuprate reagents from the side *anti* to epoxy carbon-carbon bond give π-complex **A** that lead to major *trans*-substituted cyclopropane derivatives**.** However in the case of aziridinylmalonate **6**, the *N*-protected arylsulfonyl group blocked one face of the alkenes. Hence the attack of organocuprate reagents from the less hindered face of the double bond gives complex **B** which led to *cis*-cyclopropane derivative **7**.

Scheme 2.8 Transition State Structure in the Cuprate Addition on **3** and **6**.[40]



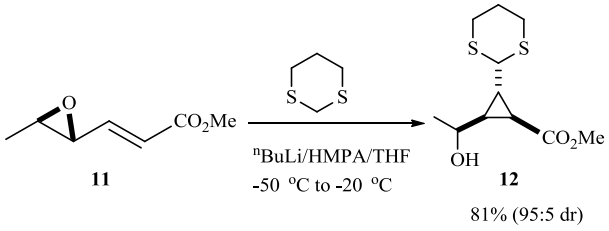
She and coworkers[24] exploited that doubly activated epoxide is not essential for the MIRC reaction of epoxy substrate with organometallic reagents. In the reaction of phenyl vinyl epoxide **9** with organolithium reagents, the phenyl group at PhCH=CH- activated the double bond towards the addition reaction. Hence the addition organolithium reagents to the carbon-carbon double bond in the presence of HMPA followed by in situ opening of epoxide give 1,2,3-trisubstituted cyclopropane derivative **10** (**Scheme 2.9**). However, the current reaction is limited to 2-alkyl-1,3-dithiane, methyl- and butyl lithium reagents affording MIRC product in high yields and moderate to excellent diastereoselectivities (80-97%, 68:32-99:1). Attempted reaction of **9** in the absence of HMPA or the use of alkyl vinyl epoxide failed under identical reaction conditions.

Scheme 2.9 MIRC Reactions of Epoxide **9** with Organolithium Reagents.[24]



On year later, the same group extended the substrate scope of the cyclopropanation reaction by effecting the MIRC reaction of dithianyllithium reagents with methyl *γ,δ* -epoxy-*α,β*-unsaturated hexenoate **11** affording corresponding product **12** in good yield and good diastereoselectivity (81%, 95:5 dr). However, attempted *trans*fer of methyl and *n*-butyl group failed under identical reaction conditions.[25]

Scheme 2.10 MIRC Reactions of **11** with Dithianyllithium Reagents.[25]

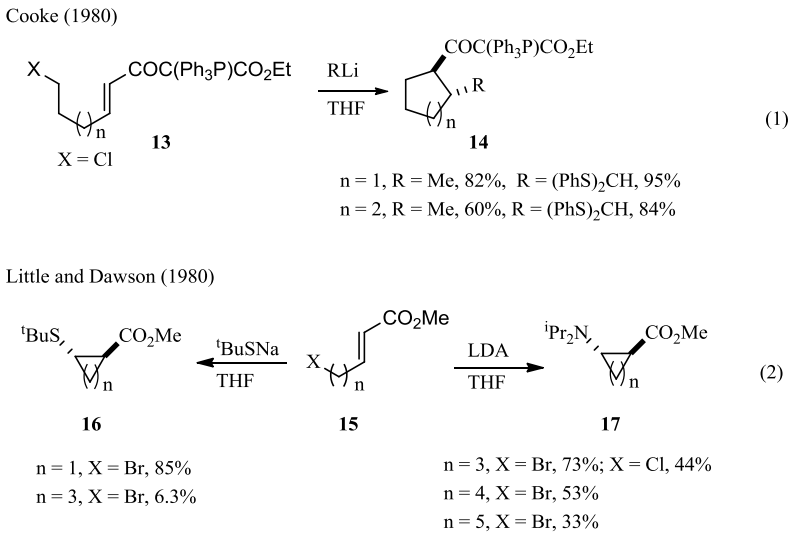


2.23.12 Halogen or Phosphate as a Leaving Group

The synthesis of cyclopropyl derivatives via MIRC reaction of organometallic reagents with *γ*-halo-*α,β*-unsaturated esters has seen numerous developments in the last few decades. In 1960, Ratney and co-workers[41] reported the first example involving the reaction of PhMgBr with methyl 4-bromocrotonate affording *trans*-2-phenylcyclopropylcarboxylic acid in poor yield (13%) after saponification. After that, two methods employing thioanions[42] and enolates[43] for

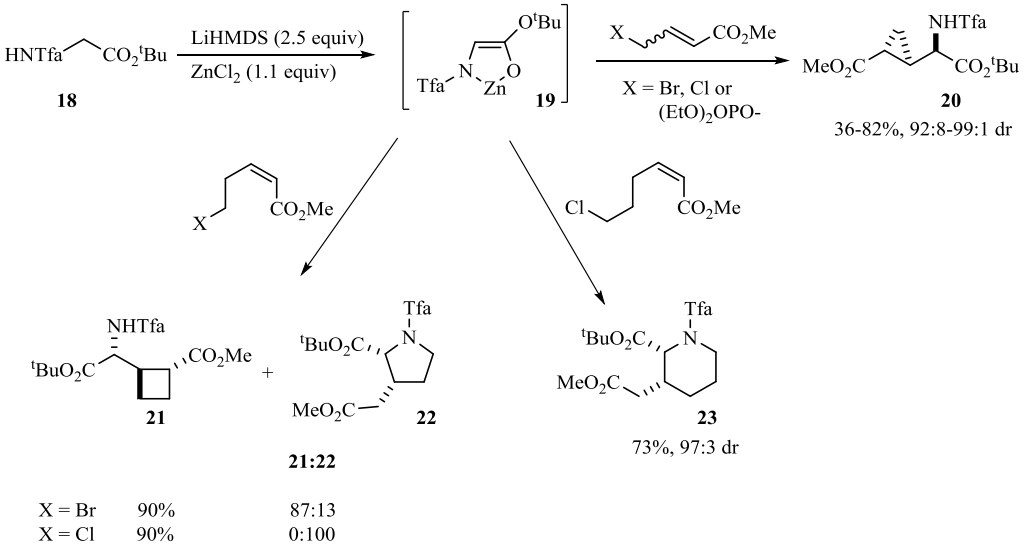
MIRC reactions with 4-halocrotonate were explored. A few examples on the involvement of methoxide,[44] cyanide[45] and carbanions[46,47] nucleophiles in the MIRC reaction with doubly activated alkylidenemalonate bearing γ-leaving groups are exist in the literature. In 1979, Cooke[48] reported MIRC reaction of organolithium reagents with $X(CH_2)_nCH=CHCOC(Ph_3P)CO_2Et$ (X = Cl, I; n = 2, 3) affording *trans* cyclopentyl- and cyclohexanyl- derivatives in moderate to good yields (**Scheme 2.11**, eqn 1, 60-95%). The exclusive formation of *trans*-product during the reaction suggested the intramolecular attack to the electrophilic carbon from the face of nucleophilic α-carbon least hindered by the β-substituent. One year later, Little and Dawson[23] reported the reaction of sulfur and nitrogen anions with $X(CH_2)_nCH=CHCO_2Me$ (X= Cl, Br, n = 1, 3, 4, 5) affording three, five, six or seven member cycloalkyl esters in poor to excellent yields (eqn 2, 23-100%). These general set of reactions as *Michael Initiated Ring Closure* (MIRC) reactions.[23] Since then, MIRC term is quite popular in the synthetic organic chemistry literature for the tandem reaction involving conjugate addition of organometallic reagents to Michael substrate followed by in situ cyclization reactions.

Scheme 2.11 Synthesis of Three, Five, Six and Seven Member Rings via MIRC Reactions.[23,48]



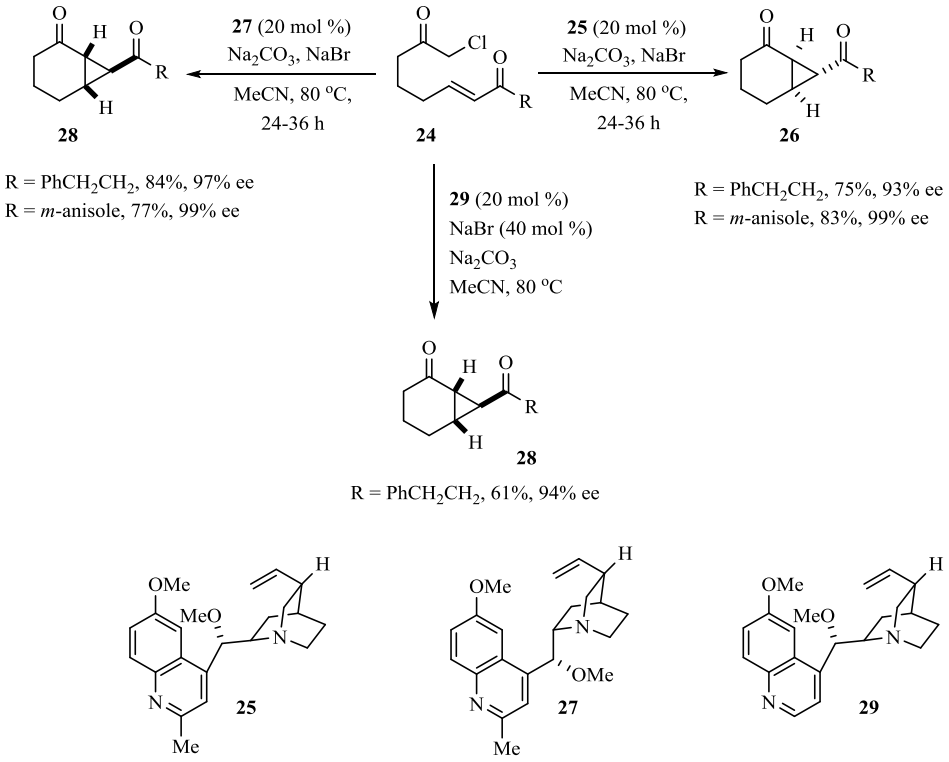
Zinc-chelated glycine ester enolates act as versatile nucleophiles in the MIRC reaction to the Michael substrates bearing *γ*-halo or phosphate leaving group and gives cyclic amino acid derivatives in high yields, diastereo- and enantioselectivity. This method can also be used for the synthesis of glutamate amino acid derivatives. Joucla and coworkers[49] are pinnoered for the MIRC reaction of lithium enolates of phenylimino glycine esters for the synthesis of cyclopropane derivatives. This methodology was later used by McIntosh group[50] and Meijere group[51] for the synthesis of 2'-substituted 2-cyclopropylglycines derivatives. Kazmaier and coworkers[52-55] successfully adapted the methodology for the MIRC reaction of zinc-chelated glycine ester enolate with enoates bearing leaving group in the allylic or homoallyic position (**Scheme 2.12**). The author claimed that 3-6 member cyclic glutamates derivatives can be synthesized in high yield and excellent diastereoselectivity by carefully optimizing the reaction conditions.

Scheme 2.12 Stereoselective Synthesis of Cyclic Aminoacid via MIRC Reactions.[52-55]



Currently, few examples on catalytic enantioselective cyclopropanation reaction of haloenoates or haloenones employing MIRC protocol were reported in the literature. Chloroketone derivatives **24** undergo enantioselective intramolecular MIRC reactions with sodium carbonate in the presence of catalytic amounts of chiral quinidine derivatives **25** affording by-cyclic compound **26** bearing three stereogenic centers in high yields (**Scheme 2.13**).[56] The mechanism of the reaction involves enantioselective *α*-deprotonation of chloroketone derivative **24** by chiral quinidine derivatives **25** to give enolate which further undergo 1,4- addition to enone and give second enolate. The intramolecular S_N2 substitution reaction of chloride anion by newly generated enolate in the cyclization step gives bicyclic derivative **26**.

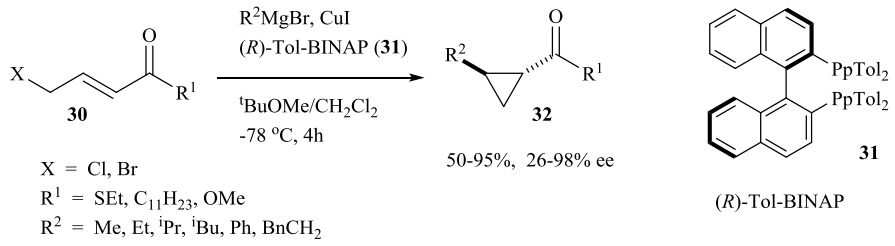
Scheme 2.13 Intramolecular Enantioselective Cyclopropanation Reactions of **24** Catalyzed by Cinchona Alkaloids. [56]



On the other hand, utilization of other enantiomer of quinidine derivative (i.e., **27**) under identical reaction conditions gives opposite enantiomer of by-cyclic compound **28**. Hence, by using a slight modification on catalytic skeleton, both enantiomer of by-cyclic derivatives **26** and **28** were synthesized in moderate yield (>70%) and good enantioselectivity (>95%). The newly reported methodology improved the yield and enantioselectivity of the *bicyclic* compound **26** than their previously established methodology employing 9-*O*-methylquinidine **29** as catalysts.[57]

Recently, Feringa and co-workers[27] reported the first and only example on enantioselective MIRC reaction of Grignard reagents with *γ*-halo-*α,β*-unsaturated esters, thioesters and ketones **30** employing procedure catalytic in copper (I) salts and chiral Tol-BINAP (**31**) (**Scheme 2.14**). A large numbers of alkyl or aryl groups can be *trans*ferred in these reactions with moderate to good yield and poor to excellent enantioselectivity of *trans*-1,2-disubstituted cyclopropane derivative **32** (up to 95% yields, up to 98% ee). This method can also be used for the synthesis of grenadamide[58] and cascarillic acids derivatives.[59]

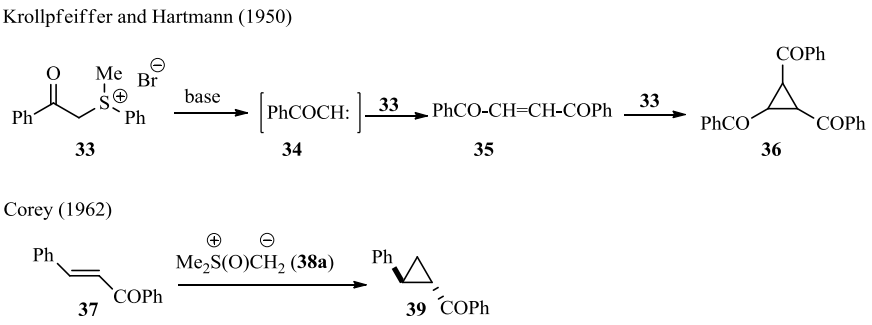
Scheme 2.14 Enantioselective MIRC Reaction of Grignard Reagents with *γ*-Halo-*α,β*-unsaturated Carbonyl Derivatives.[27]



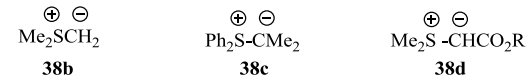
2.23 .2 MIRC Reactions Bearing Leaving Group in the Nucleophile

A variety of ylides bearing sulfonium, phosphonium, arsonium or telluronium groups as leaving group for the MIRC cyclopropanation reactions are reported in the literature. Krollpfeiffer and Hartmann[60] reported the first approach towards the synthesis of cyclopropane derivatives during the self coupling reaction of carbene generated in situ from the reaction of phenacylphenylmethyl sulfonium bromide **33** with base (**Scheme 2.15**). Self couping reaction of two molecules of **33** in the presence of base give enone **35** that undergo reaction with in situ generated carbene to give the *trans*- 1,2,3-tribenzoylcyclopropane derivatives **36**. The practical applicability of the reagent was later elaborated by Corey and coworkers[61-63] exploiting the reaction of methylene-dimethylsulfonium ylide with chalcone affording *trans*-1-benzoyl-2-phenyl-cyclopropane **39** as an exclusive product. In this reaction, $Me_2S(O)$- group present in the nucleophile acted as a leaving group.

Scheme 2.15 MIRC Reactions of Activated Alkenes with Sulfonium Ylides.[60,61-63]



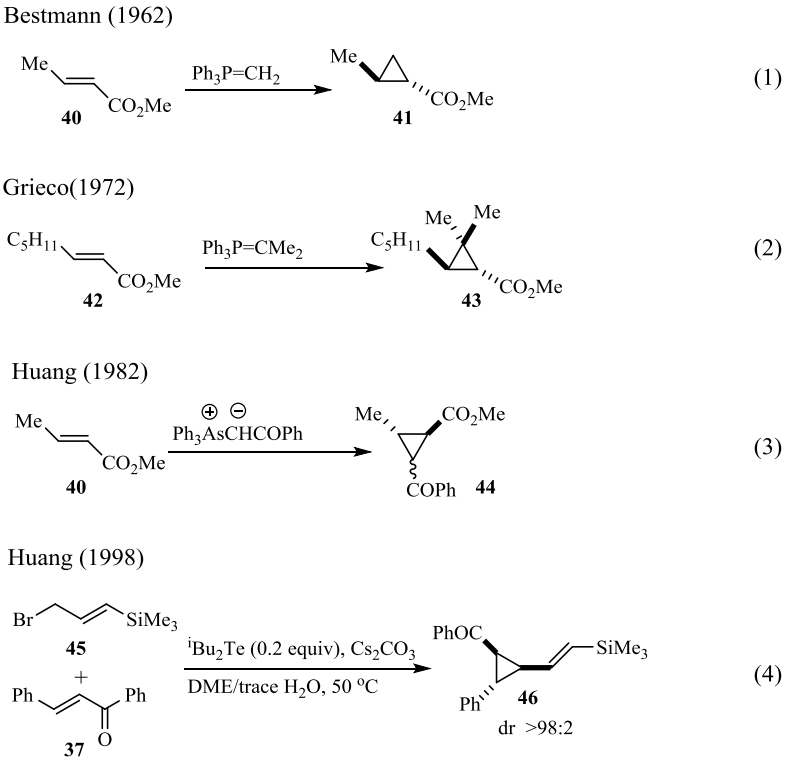
After these reports, several other gropus used sulfonium ylides for the cyclopropanation reactions. The most commonly used sulfonium ylides for the cyclopropanation reactions with alkenes and conjugated carbonyl compounds (e.g., conjugated ketones, esters and amides) are ylides **38b-38d**.[64]



38b **38c** **38d**

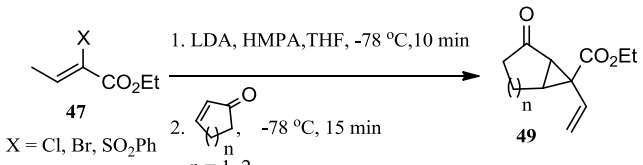
Phosphorus ylide acts as excellent nucleophile as well as leaving group for the MIRC reactions with *α,β*-unsaturated esters affording *trans*-1,2-disubsituted cyclopropane derivatives in good yields (**Scheme 2.16**). The reaction of phosphorus ylide with methyl crotonate (**40**) give *trans*-1,2-disbustituted cyclopropane derivative **41**. In this reaction, triphenyl phospine acts as a leaving group (eqn 1).[65] On the other hand, the reaction of isopropylidene-triphenylphosphorane with enoate **42** give methyl *trans*-2,2-dimethyl-3-pentylcyclopropane ester **43** (eqn 2).[66] In 1982, Huang and coworker [67] reported a new example where arsonium ylide (e.g., carbomethoxy- and benzoylmetylene triphenylarsorane) also involved in the MIRC reaction with enoates. Authors claimed that the reaction methyl crotonate **40** with arsonium ylide gives 1,2,3-trisubstituted cyclopropane derivatives **44** exclusively (eqn 3). Besides, MIRC reaction involving arsonium ylide can be extended to *α,β*-unsaturated ketones. The reaction of allylic bromide **45** with chalcone **37** in the presence of dialkyltellurium reagents also gives cyclopropanation product **46** in high diastereoselectivity (eqn 4).[68] The diastereoselectivity of cyclopropanation product holds with catalytic amounts of tellurium reagent or the application of *α,β*-unsaturated esters and amides under identical reaction conditions.

Scheme 2.16 MIRC Reactions of Activated Alkenes with Phosphonium, Arsonium and Tellurium Ylides.[65-68]



Hudlicky and co-workers[69] reported a new protocol involving the reaction of lithium dienolate dianion derived from ethyl 2-halocrotonate **47** to a variety of enones in the presence of HMPA (**Scheme 2.17**). A large number of functional groups such as Cl, Br, and SO_2Ph acts as leaving group in the cyclopropanation reactions affording low to excellent yields of by-cyclic product **49**. Their result showed that the yield and the endo/exo selectivity can be enhanced by switching the leaving group in the nucleophilic reagents. The application of bromine as leaving group gives corressponding product in quantitative yield but with poor endo/exo selectivity. On the other hand, application of $PhSO_2$- as a leaving group gives corresponding product in poor yield but with excellent endo selectivity.

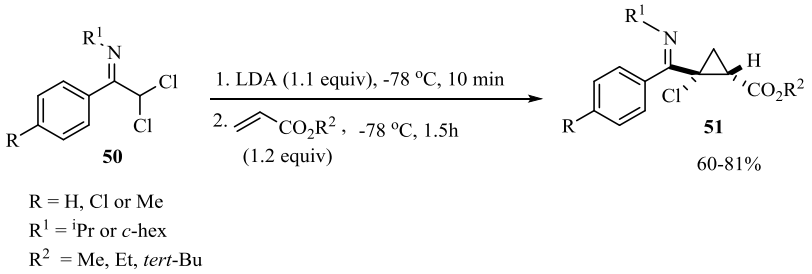
Scheme 2.17 MIRC Reactions of Lithium Enolate with Cyclic Enones.[69]



X	n	% yield	exo:endo
Br	1	100	70:30
Br	2	93	60:40
Cl	2	70	59:41
SO_2Ph	2	18	0:100

In 2005, Giubellina and Kimpe[70] reported a MIRC reaction of lithiated 3,3-dichloro-1-azaallylic anion to acrylates at low temperature affording *cis*-2-chloro-2-imidoylcyclopropanecarboxylates **51** in moderate to good yields (**Scheme 2.18**). The excellent *cis*-diastereoselection of the process was accounted due to the stereic effect. This method can be used for the synthesis of bioactive natural product midalcipran[71, 72] which is currently used as clinical antidepressant in pharmacology.

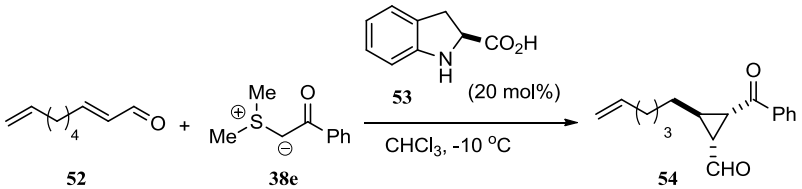
Scheme 2.18 Functionalized 2-Chlorocyclopropanecarboxylates via MIRC Reactions.[70]



In 2005, MacMillan and Kunz[73] reported the dihydroindole-2-carboxylic acid (**53**) catalyzed enantioselective MIRC reaction of dimethylphenylacyl sulfonium ylide **38e** with *α,β*-unsaturated aldehyde **52** (**Scheme 2.19**). The reaction gave cyclopropanation product **54** in good yield, diastero- and enantioselectivity (74%, 24:1% dr, 96% ee). Control experiment involving the

reaction of *N*-methylated dihydroindole-2-carboxylic acid or the use of *α,β*-unsaturated nitro, nitrile or alkylidine malonate under identical reaction conditions failed. These experimenets suggested the involvement of iminium ion intermediate in the reaction. The polarity of the solvent also played a vital role in the reaction as the rate and enantioselectivity is usually enhanced by decreasing the solvent polarity. There after, several methodologies for the proline and *N*-heterocyclic carbene (NHC) catalyzed enantioselective cyclopropanation reaction of *α,β*-unsaturated aldehydes with sulfonium ylides[74, 75] and triphenylarsonium analogues[76] were reported.

Scheme 2.19 Enantioselective Cyclopropanation Reaction of *α,β*-Unsaturated Aldehyde.[73]

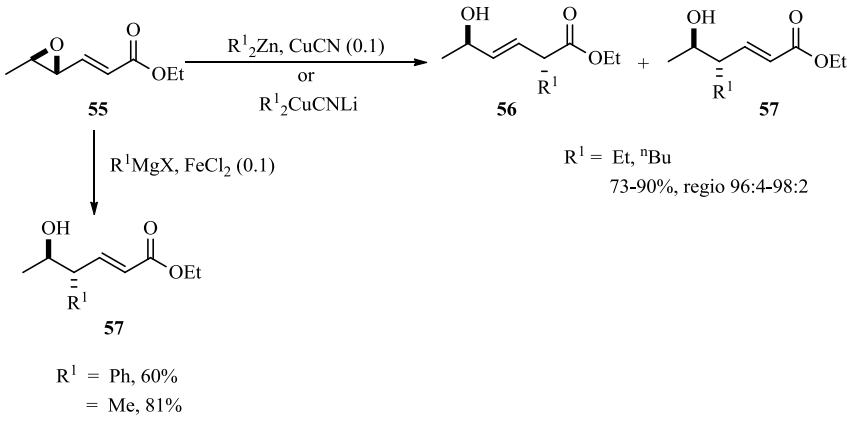


2.3 Regioselective Opening of *γ,δ*-Epoxy-*α,β*-unsaturated Esters

γ,δ-Epoxy-*α,β*-unsaturated esters are highly versatile synthons that provides opportunity for organometallic reagents to attack in one or other position leading to sevaral products. The opening of epoxide with organometallic reagent generally suffer the problem of regioselectivity due to the competitive S_N2 and S_N2' substitution reactions. Marshal investigations in the reaction of organocopper reagents on large numbers of non-conjugated, substituted and vinyl epoxides highlighted the effect of substrate in the regioselectivity of epoxide openings.[37] Organocuprate reagents derived from dialkylzinc[77] and trisubstituted epoxides[37] prefers the S_N2'substitution but usually give a mixture of *Z* and *E*- alkenes. Yatamoto[78] investigation on methyl cuprates with

methyl *γ,δ*-epoxy-*α,β*-unsaturated hexenoate showed the preferential S_N2' epoxide opening pathway. An independent study by Miyashita and coworkers[79] showed enhanced S_N2'and anti selectivity in epoxide openings when dimethylzinc reagent was used in the presence of catalytic amounts of Cu(I) salt in DMF. Recently, Dieter and Guo reported the Cu(I) salts catalyzed highly regioselective S_N2'- epoxide opening reaction of dialkyl zinc with epoxyenoate **55** (**Scheme 2.20**). The reaction gave S_N2' substituted products in good yields and excelent diastereoselectivity (up to 90 % yields and up to 98:2 % dr).[39] The excellent S_N2' regioselectivity observed in these reactions concurred well with Nakamura's computational study[80] on the involvement of alkylcyanocuprate reagents (i.e., RCu(CN)ZnR) rather than a zinc dialkylcuprate (i.e., $R_2CuZn(CN)_2$ in the allylic substitution reactions under procedure catalytic in copper. The high diastereoselectivity of the product observed in the reaction was expected due to the organocuprates preference on anti addition.[81] Hata and coworkers[33] reported a highly regioselective S_N2 opening of the epoxides using Grignard reagents in the presence of catalytic amounts of iron(II) chloride. This reaction gave anti S_N2 substitution product exclusively in good yield. The observed regioselectivity in the reactions was rationalized using a *trans*ition state model involving the formation of π-allyliron complex between organoiron reagents and olefinic part of epoxyenoate. Both of these investigations were restricted to the disubstitued epoxides bearing methyl substituent so as to pose the greatest challenges to the methodology.

Scheme 2.20 Copper and Iron Catalyzed S_N2 and S_N2' Openings of Epoxyenoate **55**.[33,39]



In summary, Michael Initiated Ring Closure (MIRC) reaction; although, not common for the functionalized allylic epoxides, possesses a keen interest of the synthetic organic chemist because of their great importance for the synthesis of cyclic moiety present in several natural products and synthetic intermediates. Among the several substrates, funtionalized α,β-unsaturated epoxides are highly attractive substrate for the synthesis of 1,2,3-substitued cyclopropane derivatives. Kasatkin and co-workers[36] attempt on MIRC reaction of organocuprate reagents with epoxyenoate **55** failed despites their successful report with epoxymalonate derivatives. She and cowokers[25] investigation was also limited to the MIRC reactions of dithianyllithium anions with epoxyenoate of methyl sorbate (i.e., **11**; *vide supra*). Hence developing a new and efficient MIRC methodology for cyclopropane reaction of organometallic reagents with epoxyenoate **55** remained relatively less explored topic in organic chemistry. Previous successful report for the regioselective S_N2'-openings of epoxyenoate **55** with organocuprate reagents in our group[39] and S_N2-openings of epoxide **55** with organoiron reagents by Hata's and coworkers[33] confined our investigation for the MIRC reaction of epoxyenoate **55** with organozincate reagents. A part of this investigation was recently published.[82]

2.4 Significance of Present Study

Although mono and dialkyl organozinc reagents play an important role in organic chemistry, they largely serve as a source of carbon nucleophiles for *trans*metallation to other metals and react with organic subsrates only in the presence of additives.[83-85] The limited reactivity of these zinc reagents has been addressed by utilization of zincate reagents[86] which display a wider range of reactivity but still often *trans*fer only one ligand and/or display limited substrate versatility. Extension of zincate reactivity profiles and development of protocols to generate them in situ using catalytic amounts of zinc salts significantly extends their synthetic utility. This is particularly so where the zincate reagents complement the reaction pathways of organometallic reagents (e.g., Cu, Pd) generated from organozinc precursors. An important example would be regio-divergent pathways on highly functionalized substrates able to undergo multiple reactions where zincates would favor conjugate addition while cuprates favored S_N2'- allylic substitution.

Although cuprate conjugate additions play a prolific role in organic synthesis, the difficulty of trapping the resultant enolate remains a limitation of the method.[87] The earlier protocol of increasing solvent polarity by addition of HMPA[88] has been complemented recently by exploitation of zinc enolates resulting from copper catalyzed 1,4-additions of organozinc reagents.[89,90] The three-component coupling involving zincate conjugate addition to cyclopentenones followed by alkylation of the zinc enolate amply demonstrates the effective utility of the strategy.[91] Development of zincate mediated reactions leading to zinc enolates provides new opportunities for tandem reactions involving enolate alkylations and carbozincations of proximate alkenes.[92] Our work on novel zincate promoted MIRC reactions indicate a continuing need to understand underlying dynamics of zincate-substrate reactivity profiles, which have been less extensively explored than Cu and Pd reagents.

The immediate application of the proposed work on MIRC reactions lies in the stereo- and regio-controlled synthesis of cyclopropane derivatives,[82] which are important in both synthesis[93] and medicinal chemistry.[94-98] This is illustrated by recent reviews on enantioenriched cyclopropanes,[99] fluorinated-,[100] alkylidene-,[101] silylmethyl-substituted-,[102] spiroannulated-, and arylcyclopropanes,[94] and the preparation and biological activity of cyclopropyl phosphonates,[95] cyclopropane derived peptidomimetics,[96] and cyclopropyl-containing α-amino acids.[97, 98]

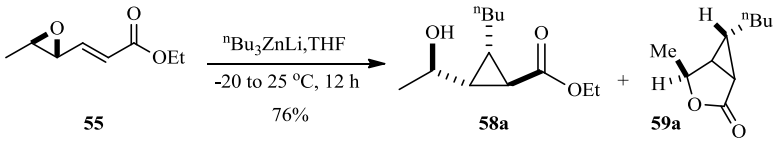
2.5 Results

2.51 MIRC Reactions of *γ,δ*-Epoxy-*α,β*-enoates 55

The initial effort for the present study was focused on investigating S_N2 opening reaction of organozincate reagents with epoxyenoate **55** using the reaction conditions previously established by Alexakis and co-workers for the regioselective opening of cyclic and acyclic non-functionalized epoxides.[34] The reaction of lithium tributylzincates with epoxyenoate **55** under argon in THF gave two products as moniterred by thin layer chromatography. The ^1H and ^{13}C NMR spectra of the crude product confirmed that reaction did not proceed via expected S_N2 or S_N2'-epoxide opening pathway (i.e., product showed the absence of olefinic hydrogens and carbons in ^1H and ^{13}C NMR respectively). This result quickly ascertained that the reaction was not general and hence needed further investigation. Purification of products followed by 45^o, 90^o and 135^o DEPT NMR of the major product showed the presence of three methyl, four methylene, four methine and one quaternary carbon atoms. The infrared spectrum showed a broad peak at 3457 cm^{-1} and a sharp singlet at 1724 cm^{-1} corresponding to hydroxyl and ester functional groups respectively. The GC/MS spectrum of the compound showed a molecular ion (M^+) peak at 214 amu and prominent $M\text{-}H_2O]^+$ peak at 196 amu. All of these data supported the formation of 1,2,3-trisubstituted cyclopropyl derivative **58a** resulting from the MIRC reaction of epoxyenoate **55** with lithium tributylzincate reagents (**Scheme 2.21**). The ^1H, ^{13}C, and 45^o, 90^o and 135^o DEPT NMR of the minor product showed the presence of two methyl, three methylene, four methine and one quaternary carbon atoms. The carbonyl carbon in the minor product was more down fielded than that in the major product. Infrared spectrum of the product showed a sharp singlet at 1753 cm^{-1} corresponding to ester functional groups but the absence of broad peak corresponding to –OH group. The GC/MS of the minor product showed molecular ion (M^+) peak at 168 amu.

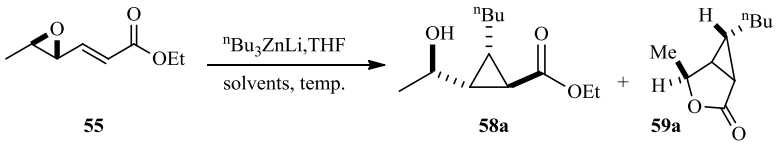
All of these results supported the bicyclic structure **59a** of minor product and their final identity was confirmed by comparing NMR data with the literature one.[103]

Scheme 2.21 MIRC Reactions of Epoxyenoate **55** with Lithium Tributylzincates.



In order to substantiate the conjugate addition reaction from cyclization, a temperature profile study of the reaction was carried out. The reaction of organozincates with **55** did not initiate at -78 °C in THF (**Table 2.1**, entry 1), was extremely slow at -55 °C (entries 2 and 3) and occurred at reasonable rate at -35 °C (entry 4). The best yield was observed while running reaction at -20 °C in THF for 2 hours (entry 7). The reaction could also be carried out at higher temperatures (e.g., -10 °C), however yield and diastereoselectivity of the major product **58a** was diminished in the expense of increased yield of bicyclic lactone **59a** (entry 8). Utilization of lithium tributylzincates in Et_2O again gave excellent yields and diastereoselectivities (entry 9). Surprisingly, performing reaction in non-coordinating solvent (e.g., CH_2Cl_2) reversed the diastereoselectivity and gave bicyclic lactone **59a** exclusively (entry 10). In no instance, could the conjugate addition reaction be disentangled from the epoxide opening reaction indicating rapid cyclopropane formation from the resultant enolate anion.

Table 2.1 Temperature and Solvent Study on MIRC Reactions of *γ,δ*-Epoxy-*α,β*-enoate **55** with Lithium Tributylzincate.[82]



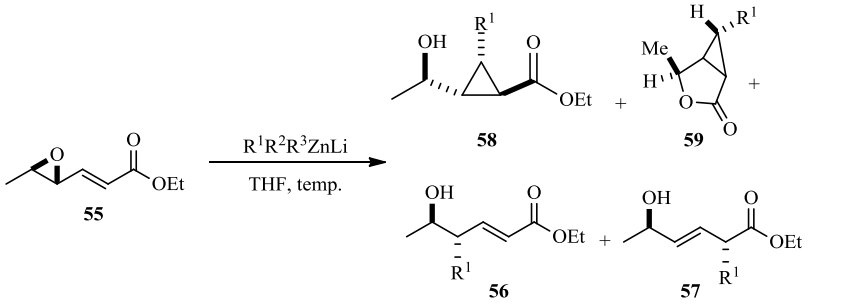
entry	temp (°C)[a]	time (h)	solvent	**55**:**58**:**59**[b]	% yield (**58a**+**59a**)[c]	dr **58a**[d]
1	-78	3	THF	100:0:0	-	-
2	-55	2	THF	60:40:0	-	-
3	-55	4	THF	45:1:0	-	-
4	-35	3	THF	0:94:6	79	96:4
5	-20	0.5	THF	16:72:12	-	-
6	-20	1	THF	2:93:5	-	-
7	-20	2	THF	0:95:5	82	96:4
8	-10	0.75	THF	0: 92:8	77	94:6
9	-20	3	Et_2O	0:98:2	81	97:3
10	-20	3	CH_2Cl_2	0:0:100	82	-

[a] The reactions were carried out at the indicated temperatures for the specified time unless otherwise noted. [b] The ratio was determined by integration of ^{1}H-NMR absorption peaks of carbinol hydrogen or via peak heights of ^{13}C-NMR absorption peak of olefinic carbon. DEPT NMR experiments established the cyclopropane composition for each diastereomers. [c] Yields are based upon isolated products purified by column chromatography. [d] Diastereomeric ratios were determined from ^{1}H-NMR integration of the carbinol hydrogen or via peak heights of ^{13}C-NMR absorptions of the carbinol carbon.

With optimized reaction conditions in hand, the MIRC reaction of wide numbers of alkyl, alkenyl, alkynyl, and heteroaryl zincate reagents with epoxyenoate **55** was investigated (**Table 2.2**). Utilization of mix organozincates (1.0 equiv) such as ^{n}BuZnMe$_2$Li, ^{n}BuZnMe^{t}BuLi or ^{n}BuZn^{t}Bu$_2$Li in THF gave **58a** as a major product in good yields and good to excellent diastereoselectivity (entries 1-3) along with minor bicyclic lactone **59a**. In these entire reactions, ^{n}Bu group acted as *trans*ferring ligand and both Me or ^{t}Bu acted as non*trans*ferring ligands while using in various combinations. Tranfer of ^{n}Bu group generally gave two cyclopropane products as evidenced by DEPT NMR, with very high diastereoselectivity. The relative stereochemistry of

the major isomer **58a** was established by X-ray crystallography (vide infra) while minor isomer is unlikely to be diasteromer leading to **59a** since we were unable to convert **58a** into **59a** and vice versa. When 1-hexyne was employed as a non-*trans*ferable ligand under otherwise identical conditions, the course of the reaction altered leading to inseparable mixtures of S_N2- and S_N2'-epoxide opening products (entry 4).

Table 2.2. Reaction of Mixed Triorganozincates with *γ,δ*-Epoxy-*α,β*-enoate **55**.[82]



a R^1 = ^{n}Bu **c** R^1 = Me (**c'** R^1 = Me-D_3)
b R^1 = ^{i}Pr **d** R^1 = 2-furyl

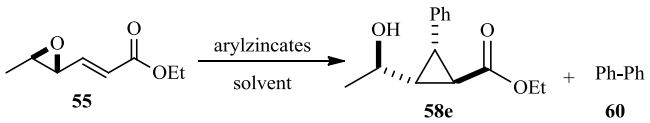
entry	R^1	R^2	R^3	temp. °C (h)[a]	% yield[b] **58**	**59**	**56:57**	dr **58**[c]
1	^{n}Bu	Me	Me	-20 (3)	71	5	-	98:2
2	^{n}Bu	Me	^{t}Bu	-20 (4)	83	-	-	100:0
3	^{n}Bu	^{t}Bu	^{t}Bu	-20 (4)	70	-	-	97:3
4	^{n}Bu	C_6H_9[d]	C_6H_9[d]	-20-rt (12)	-	-	56[e]	-
5	^{i}Pr[f]	Me	Me	-20 (6)	69	-	18[g]	100:0
6	Me	Me	Me	0-rt (12)	65	-	-	100:0
7	CD_3	CD_3	CD_3	0-rt (12)	67	-	-	97:3
8	2-furyl	Me	Me	-20-rt (12)	-	-	57[i]	-
9	2-thiophenyl	Me	Me	0-rt (12)	-	-	33[g]	-
10	pyrollidinyl	Me	Me	0-rt (12)	SM	-	-	-
11	2-pyran	Me	Me	-20-rt (12)	SM	-	-	-

[a] Reactions were run in THF at indicated temperatures and quenched at that temperatures unless otherwise noted. [b] Yields are based upon isolated products purified by column chromatography. [c] Diastereomeric ratio was determined from ^{1}H-NMR integration of carbinol hydrogen or via peak heights of ^{13}C-NMR absorptions of carbinol carbon. The minor diasteromer is either **112** or **113** (Scheme 2.28, R = ^{n}Bu). [d] C_6H_9 = 1-hexynyl. [e] Isomer ratio of **56:57** = 76:24. [f] Magnesium zincate was employed. [g] An inseparable 1:1 mixture of regioisomer **56:57** was obtained. [i] The ratio of **56:57** >95:5 and **57** was not detected in the NMR spectrum. Reprinted with permission from *J. Org. Chem.* **2013**, *78*, 12426-12439. Copyright (2013), American Chemical Society.

The isopropyl group *trans*ferred well but gave significant amounts of S_N2 and S_N2'-epoxide opening products along with major cyclopropane **58c** (entry 5). Utilization of the less reactive lithium trimethylzincate although *trans*ferred the methyl group, it indeed needed a higher temperature and longer reaction time for the completion of reaction (entry 6). Reaction of deuterated lithium trimethylzincate under the identical reaction conditions gave similar yields of MIRC product (entry 7). 2-Furyl group from lithium dimethylfurylzincate *trans*ferred in mixed solvent systems (nitro methane/THF; 1:1) affording moderate yields of S_N2-epoxide opening product (entry 8). Although, the Me-group from lithium dimethylthiophenylzincates get *trans*ferred to the **55** affording the mixture of S_N2 and S_N2'- epoxide openings product in poor yield (entry 9), utilization of lithium dimethylpyrollidinylzincate and lithium dimethyl-2-pyranyl zincate with epoxyenoate **55** failed under identical conditions (entry 10 and 11). Products **56a-c** and **57a-c** were characterized by comparing their NMR spectra with the known compounds. [39]

Our encouraging results on the MIRC reaction of mix alkylzincates with epoxyenoate **55** prompted us to investigate the reaction of arylzincates under identical reaction conditions. Unlike trialkylzincates, the reaction of triaryl or mix alkylarylzincates with epoxyenoate **55** gave none to low yield of cyclopropane products (**Table 2.3**, 0-32%). The major product isolated in these reactions was biphenyl arising from the self coupling reaction (37-89%). Attempted effort to suppress the biphenyl formation employing coordinating (e.g, THF, Et_2O) or non-coordinating (e.g., CH_2Cl_2, toluene) solvents failed. The formation of biphenyl could not be suppressed by using mix solvent system (entry 2) or using catalytic amounts of Lewis acid ($MgCl_2$) as additives (entry 4). These results confirmed that aryl zincates underwent self-coupling reaction before reaction with epoxyenoate **55**. Our result was consistent with literature report where $ZnBr_2$ was used as homocoupling reagents for the arylmagnesium halide leading to the formation of symmetrical biaryal compounds.[104]

Table 2.3 Reaction of Arylzincates with Epoxyenoate **55**.

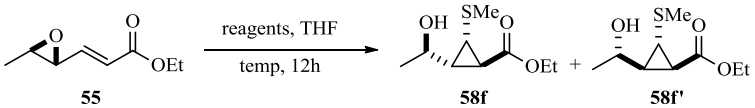


entry	organozincates	solvent	temp ^{o}C, (time, h)	% yield[a] **58e**	**60**
1	$PhMe_2ZnLi$	THF	-20 to rt (12)	-	77
2	$PhMe_2ZnLi$	THF:$MeNO_2$[b]	-20 to rt (12)	-	74
3	$PhMe_2ZnLi$	Et_2O	-20 to rt (12)	32	37
4	$PhMe_2ZnLi$[c]	Et_2O	-20 to rt (12)	-	63
5	$PhMe_2ZnLi$	CH_2Cl_2	-20 to rt (12)	-	68
6	$PhMe_2ZnLi$	toluene	-20 to rt (12)	-	71
7	Ph_3ZnLi	Et_2O	-20 to rt (12)	-	89
8	$PhMe_2ZnMgCl$	Et_2O	0 to rt (12)	-	85

[a] Yields are based upon isolated products purified by column chromatography. [b] Organozincates were prepared in the mixture of THF and $MeNO_2$ (1:1). [c] 0.33 equiv. of anhydrous $MgCl_2$ was used in the reaction.

Attempted reaction of lithium trimethylthiolatozincates with **55** gave the MIRC products in good yields but with no diastereoselectivity (**Scheme 2.22**). The application of lithium dimethylmethylthiolatozincate or sodium thiomethoxide also gave similar yields and again with no diastereoselectivity.

Scheme 2.22 Heteroatom Induced MIRC Reactions.

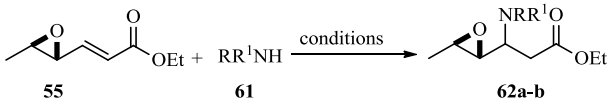


$(MeS)_3ZnLi$	-60 to rt	90% (1:1)
$Me_2ZnSMeLi$	-40 to rt	78% (1:1)
MeSNa	-40 to rt	83% (1:1)

Amines **61a-b** can also undergo conjugate addition reactions to epoxyenoate **55** to give 1,4-adduct **62a-b** without cyclopropanation under microwave irradiation (**Table 2.4,** entries 1-2).

Running the reaction at refluxing conditions in methanol did not improve the diastereoselectivity of 1,4-adduct (entry 3). The reaction of pyrollidine with epoxyenoate **55** in the absence of solvent at room temperature also give poor diastereoselective 1,4-adduct (entry 4). Although the relative configuration of these stereoisomers for **62** remained to be established, the examination of reaction conditions and various metal thiolates and amides can be carried out to improve diastereoselectivity in future. Besides, the treatment of **62** with LDA followed by S_N2 opening of epoxides with enolate may lead to cyclopropanation products.

Table 2.4 1,4-Addition of Alkyl Amines on Epoxyenoate **55**.



55 **61** **62a-b**

a R = $PhCH_2$ R^1 = H

b R, R^1 = $-CH_2(CH_2)_2CH_2-$

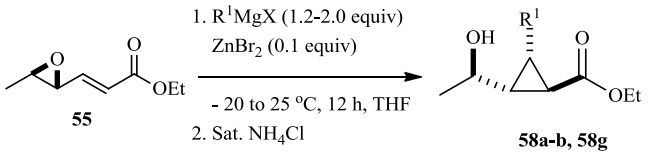
entry	RNH_2 (equiv.)	conditions (time, h)[a]	product	**%** yield (dr **62**)[b]
1	$BnNH_2$ (1.0)	mw, 50% power (0.83)	**62a**	79 (67:33)
2	$BnNH_2$ (1.0)	mw, 20% power (2)	**62a**	83 (67:33)
3	$BnNH_2$ (1.0) [c]	MeOH, reflux (12)	**62a**	67 (67:33)
4	pyrollidine (1.2)	rt (48)	**62b**	77 (70:30)

[a] Microwave reactions were carried out in the absence of solvents unless otherwise noted. [b] Yields are based upon isolated compounds purified by column chromatography. [c] Reaction was carried out in the presence of methanol.

2.52 Catalytic Procedure in MIRC Reaction

In an effort to minimize the amount of organometallic reagents used for the MIRC reactions, a procedure catalytic in zinc bromide employing Grignard reagents was investigated. Control experiment involving the reaction of ^{n}BuMgCl (1.1 equiv) with epoxide **55** gave a complex mixture along with the complete consumtion of starting materials. GC/MS spectrum of the crude reaction mixtureshowed four major compounds. Two of those compounds showed molecular ion peaks at 212 amu corresponding for S_N2 and S_N2' epoxide openings products and remaining two compounds showed molecular ion peaks at 226 amu corresponding to *n*-butyl ketone derivatives. A minor amount of unidentified impurities was also observed in the reactions. On the other hand, the reaction of ^{n}BuMgCl with epoxide **55** in the presence of $ZnBr_2$ (0.1 equiv) gave cyclopropanation product **58a** in good yield and excellent diasteroselectivity (**Table 2.5**, entries 1 and 3). The presence of TMSCl did not change the yield and diastereoselectivity of the MIRC products (entry 2). The reaction of *iso*-propyl- or ethyl Grignard reagents (1.2 equiv) with epoxyenoate **55** in the presence of catalytic amounts of $ZnBr_2$ (0.1 equiv) also gave MIRC products **58b** and **58g** respectively in good yields and excellent diastereoselectivity (entries 4-6, dr 100:0). In fact, the reaction of Grignard reagents with epoxide **55** in the presence of catalytic amounts of $ZnBr_2$ gave significantly better chemical yield and better diastereoselectivity than the procedure employing stoichiometric in zincate reagents (**Table 2.1,** entry 7 vs **Table 2.5**, entries 1-3). However, attempted reaction of the methyl, vinyl and phenyl Grignard reagents with **55** under identical reaction conditions failed.

Table 2.5 Zinc Bromide Catalyzed MIRC Reactions of Grignard Reagents with **55**.



Entry	R^1 (equiv)	product	% yield[a]	dr **58**
1	^{n}Bu (2.0)	**58a**	85	100:0
2	^{n}Bu (2.0)[b]	**58a**	85	100:0
3	^{n}Bu (1.2)	**58a**	85	100:0
4	^{i}Pr (1.2)	**58b**	80	100:0
5	^{i}Pr (1.2)	**58b**	78	100:0
6	Et (1.2)	**58g**	73	100:0
7	Me (1.2)	-	-	-
8	CH_2=CH(1.2)	-	-	-
9	Ph (1.2)[c]	-	-	-

[a] Yields are based upon isolated products purified by column chromatography. [b] 2.0 equiv. of TMSCl was added. [c] ~ 45% of biphenyl was observed.

2.52 Substrate Scope in MIRC Reaction

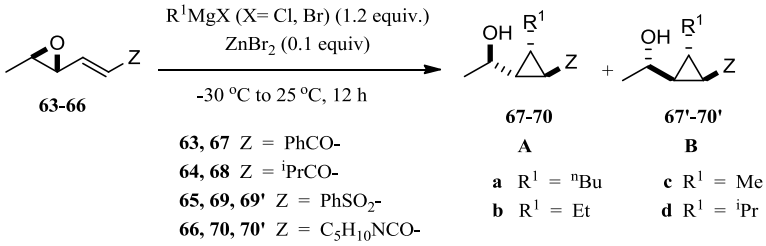
After establishing the optimize conditions for the diastereoselective MIRC reactions of in situ generated magnesium organozincates with epoxyenoate, the catalytic procedure was screened with epoxyenones (**63** and **64**), epoxyensulfone (**65**) and epoxyenamide (**66**). The requisite epoxides **63-66** used for the reaction were synthesized by slight modification of the literature procedures (see detailed in experimental section).[105-108]

The reaction of *γ,δ*-epoxy-*α,β*-unsaturated phenyl ketone **63** with ^{n}BuMgCl (1.2 equiv) in the presence of catalytic amounts of $ZnBr_2$ in THF gave MIRC product **67a** in moderate yield but with excellent diastereoselectivity (**Table 2.6**; entry 1, 67%, dr 100:0). Utilization of non-coordinating solvents (i.e., CH_2Cl_2) also offered the similar yield and diastereoselectivity (entry

2). In both of these reactions, minor unidentified byproduct mixture (5-10%) was also observed. The separation of the byproduct mixture using column chromatography was unsuccessful however GC/MS spectrum of the unidentified mixtures showed four major peaks. One set of these compounds showed molecular ion peak (M^+) at 246 amu corresponding to S_N2 and S_N2'- epoxide opening products while the remaining two compounds showed molecular ion peaks (M^+) at 304 amu consistent with the 1,2-addition of organozincate/Grignard reagents to the carbonyl carbon before or after the completion of S_N2 and S_N2'- epoxide opening reactions. Although, EtMgBr (1.2 equiv), MeMgCl (1.2 equiv) or ^{i}PrMgCl (1.2 equiv) in both coordinating and non-coordinating solvents gave similar yields and diastereoselectivity of MIRC product (entries 3-7), the reaction of ^{t}BuMgCl (1.2 equiv) failed under identical conditions (entry 8). Interestingly, the reaction of ^{n}BuMgCl (1.2 equiv) with *γ,δ* -epoxy-*α,β*-unsaturated isopropyl ketone **64** in the presence of catalytic amounts of $ZnBr_2$ in both coordinating (e.g., THF) and non-coordinating (e.g., CH_2Cl_2) solvents gave the MIRC product **68a** in excellent yields and diastereoselectivities (entries 9-10). Although, the reaction of MeMgCl only gave a trace amount of MIRC product at room temperature (entry 11), employment of ^{i}Pr- or ^{t}BuMgCl gave MIRC product in excellent yield and excellent diastereoselectivity under identical reaction conditions (entries 12 and 13 respectively).

Surprisingly, chemical yield and diastereoselectivity in the reaction of *γ,δ* -epoxy-*α,β*-unsaturated phenyl sulfone **65** with insitu generated zincates depends upon the solvent employed. The employment of catalytic procedure in the reaction of ^{n}BuMgCl with epoxy ensulfone **65** in THF gave the MIRC product in good yield but with poor diastereoselectivity (entry 14, 78%, dr 58:42). The utilization of non-coordinating solvents such as CH_2Cl_2 or toluene under identical condtions completely reversed the diastereoselectivity of the cyclopropyl sulfone (entries 15, 16). The single diastereomer of the cyclopropyl sulfone **69a'** observed in non-coordinating solvents

Table 2.6 MIRC Reactions of Alkyl Grignard Reagents with Epoxides **63-66**.[82]



entry	epoxide	R	solvent	% yield [a]	dr (**A:B**) [b]
1	**63**	^{n}Bu	THF	67[c]	100:0
2	**63**	^{n}Bu	CH_2Cl_2	66[c]	100:0
3	**63**	Et	THF	63[c]	100:0
4	**63**	Et	Et_2O	63[c]	100:0
5	**63**	Et	CH_2Cl_2	61[c]	100:0
6	**63**	Me	THF	57[c]	100:0
7	**63**	^{i}Pr	THF	63[c]	100:0
8	**64**	^{t}Bu	THF	trace	-
9	**64**	^{n}Bu	THF	88	100:0
10	**64**	^{n}Bu	CH_2Cl_2	85	100:0
11	**64**	Me[d]	THF	trace	-
12	**64**	^{i}Pr	THF	82	100:0
13	**64**	^{t}Bu	THF	82[e]	100:0
14	**65**	^{n}Bu	THF	78	58:42
15	**65**	^{n}Bu	CH_2Cl_2	83	0:100
16	**65**	^{n}Bu	PhMe	89.5	0:100
17	**65**	Me	THF	trace[f]	-
18	**65**	Me	PhMe	83	7:93
19	**65**	^{i}Pr	THF	trace[f]	-
20	**65**	^{i}Pr	PhMe	87	0:100
21	**64**	^{t}Bu	PhMe	trace[f]	-
22	**66**	^{n}Bu	THF[g]	48	59:41
23	**66**	^{n}Bu	Et_2O[g]	55	53:47
24	**66**	^{n}Bu	PhMe[g]	63	36:64
25	**66**	^{n}Bu	CH_2Cl_2[g]	52	27:73

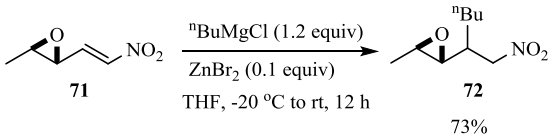
[a] Yields are based upon isolated products purified by column chromatography and reflect the sum of both diastereomer. [b] Diastereomeric ratio was determined from ^{1}H-NMR integration of the carbinol hydrogen or via peak heights of ^{13}C-NMR absorptions of the carbinol carbon. [c] Minor amounts (5-10%) of unidentified byproducts mixture was also isolated in the reaction. [d] Reaction ran at room temperature for 30 hours but only a trace product was observed. [e] Utilization of $^{t}Bu_3ZnLi$ in THF gave 73% yield of single product. [f] Starting material (~90%) was recovered. [g] Minor amounts of unidentified product mixture was also isolated.

(e.g., CH_2Cl_2 or toluene) was in fact a minor product observed in THF. Although, the reaction of Me- and ^{i}Pr- with epoxyensulfone **65** gave trace amounts of MIRC product in THF (entries17 and 19 respectively), the reaction in CH_2Cl_2 gave MIRC products **69c'** and **69d'** in excellent yield and excellent diastereoselectivity (entries 18 and 20, 83% vs 87%, dr 100:0 respectively). ^{t}BuMgCl did not react with epoxyensulfones **65** under identical reaction conditions.

The reaction of ^{n}BuMgCl with epoxy enamide **66** in THF or Et_2O gave moderate yields of MIRC products **70a** and **70a'** but with poor diastereoselectivity (entries 22 and 23, 48% vs 55%, 59:41 vs 53:47 dr). Utilization of the non coordinating solvents such as CH_2Cl_2 or toluene also did not significantly improve the diastereoselectivity (entries 24-25). Given the poor diastereoselectivity in the reaction of ^{n}BuMgCl with epoxyenamide **66** under previously optimized reaction conditions, further investigation with other alkyl Grignard reagents was abandoned in lieu of an extensive screen of the protocol.

The next functionalized allylic epoxides investigated for the reaction of alkyl Grignard reagents using procedure catalytic in zinc bromide was *γ,δ*-epoxy-*α,β*-unsaturated nitro compound **71** (**Scheme 2.23**). Although *n*-butyl group underwent 1,4 conjugate addition to the nitrodiene under previously optimized condition, the in-situ cyclization of the nitroenolate failed affording 1,4-conjugate adduct **72** in moderate yield.

Scheme 2.23 1,4-Conjugate Addition to Epoxynitroalkene.

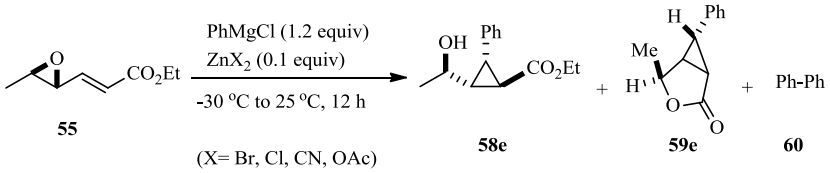


2.54 MIRC Reactions of Phenylmagnesium Bromide with Epoxides 55, 63, 64, 65 and 66

The optimized catalytic procedure established in the reaction of alkyl Grignard reagents with epoxides **55, 63, 64, 65** and **66** was next applied for the MIRC reaction with PhMgBr. The addition of epoxyenoate **55** to the mixture of PhMgBr (1.2 equiv) and $ZnBr_2$ (0.1 equiv) in coordinating (e.g., THF or Et_2O) or non-coordinating (CH_2Cl_2 or toluene) solvents gave biphenyl byproduct exclusively. The competitive formation of biphenyl was minimized by the reverse addition of PhMgBr reagents, zinc salt and epoxyenoate **55** (i.e., addition of PhMgBr (1.2 equiv) to the mixture of zinc salts (0.1 equiv) and epoxyenoate **55** (1.0 equiv) under argon in the solvent under study). Although the reverse addition of PhMgBr in THF could not suppress the biphenyl formation and gave only the trace amounts of MIRC product (**Table 2.7**; entry 1), performing reaction in Et_2O at 0 ^oC gave cyclopropanation product **58e** in moderate yields (entry 2, 59%) along with minor bicyclic lactone **59e** (5%) and reduced amounts of biphenyl (30%). The slow addition of PhMgBr to the mixture of **55** and zinc bromide at room temperature offered similar yield of MIRC products (entry 3). Although, the dilution of Grignard reagent with Et_2O followed by slow addition lowered the formation of biphenyl, the yields of MIRC product also lowered (entry 4). The addition of catalytic amounts of $Ni(acac)_2$ followed by slow addition of Grignard reagents significantly increased the yield of MIRC product **58e** with diminished amounts of biphenyl (entry 5). Utilization of non-coordinating solvent (e.g., CH_2Cl_2 or toluene) in the catalytic procedure further lowered the yield of cyclopropanation product **58e** in the expense of increased yield of bicyclic lactone **59e** (entries 6 and 7). Unlike the reaction of $^nBu_3ZnLi$ with epoxyenoate **55**, the exclusive formation of bicyclic lactone **59e** was not achieved while running the reaction in CH_2Cl_2 (entry 6). The higher yield of the cyclopropanation products and diminished formation of biphenyl in Et_2O suggested the role of the solvent in the reaction. Hence further screening of the MIRC reaction was carried out in Et_2O. Utilization of catalytic amounts

of $ZnCl_2$, ZnI_2 or $Zn(OAc)_2$ under the previously optimized conditions in Et_2O also gave the similar yield of the cyclopropanation product **58e** and biphenyl by-product **60** (entries 8, 9 and 10 respectively). Surprisingly, utilization of $Zn(CN)_2$ (0.1 equiv) retained the yield of cyclo-propanation product **58e** with diminished amounts of biphenyl byproduct (entries 11 and 12).

Table 2.7 $ZnBr_2$ Catalyzed MIRC Reaction of PhMgBr with Epoxyenoate **55**.[82]



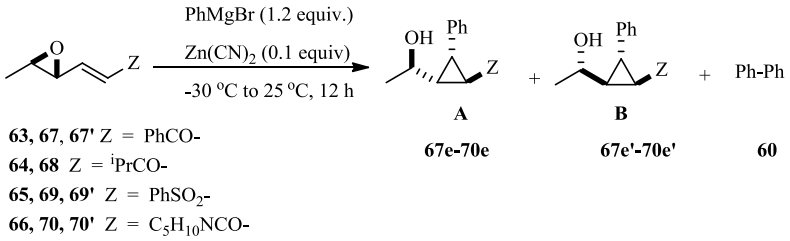
entry	zinc salt (0.1 equiv)	solvent	temp °C (h)	% yield[a] **58e**	% yield[a] **59e**	**58e:59e** (range)[b]	% yield[a] **60**
1	$ZnBr_2$	THF	rt (12)	trace	-	-	42
2	$ZnBr_2$	Et_2O	0 to rt (12)	59	5	83:17 (11)	30
3	$ZnBr_2$[c]	Et_2O	rt (12)	48	5	80:20 (7)	37
4	$ZnBr_2$[d]	Et_2O	rt (12)	46	4	83:17 (11)	22
5	$ZnBr_2$[e]	Et_2O	rt (12)	63	3	86:14 (1)	17
6	$ZnBr_2$	CH_2Cl_2	rt (12)	32	31	68:32 (15)	26
7	$ZnBr_2$	PhMe	rt (12)	45	17	68:32 (9)	27
8	$ZnCl_2$	Et_2O	rt (12)	57	7	70:30 (8)	28
9	ZnI_2	Et_2O	rt (12)	59	3	84:16 (3)	31
10	$Zn(OAc)_2$	Et_2O	rt (12)	52	5	84:16 (6)	25
11	$Zn(CN)_2$	Et_2O	rt (12)	61	7	86:14 (6)	6
12	$Zn(CN)_2$	Et_2O	rt (1.5)	61	3	78:22 (3)	5
13	$Zn(CN)_2$[f]	Et_2O	0 to rt (2)	49	17	63:37 (5)	13
14	$Zn(CN)_2$[g]	Et_2O	-20 to rt, (4)	37	33	44:46 (5)	11

[a] Yields are based on isolated products purified by column chromatograpy. [b] Diastereomeric ratio was determined by averaging values from integration of the ^1H NMR absorptions of the methyl attached to the carbinol carbon, the benzyl methine proton, and the ^{13}C-NMR peak heights of the carbonyl carbon absorption. The range between the high and low value for the major diastereomer was also given and ranges between 3 and 16. [c] Grignard reagent was added to the substrate at room temperature over 15 mins. [d] Grignard reagent was diluted with 3.0 mL of Et_2O and added over 15 mins at room temperature. [e] $Ni(acac)_2$ (0.1 equiv.) was added to the zinc salt before adding Grignard reagent. [f] LiCl (0.2 equiv) was added to the mixture of zinc salts and epoxyenoate **55** before adding Grignard reagent at 0 °C. [g] Grignard reagent was diluted with anhydrous Et_2O and added to the zinc salt-epoxide mixture over 30 mins at -20 °C.

The addition of catalytic amounts of LiCl to the mixture of $Zn(CN)_2$ and epoxide (entry 13) or the dilution of Grignard reagents followed by addition to the mixture of $Zn(CN)_2$ and epoxide at lower temperature significantly lowered the yield of cyclopropane products **58e** in the expense of increased yield of bicyclic lactone **59e** (entry 14).

The good yield of MIRC product and reduced amounts of biphenyl in the reaction of PhMgBr with epoxyenoate **55** prompted us to use zinc cyanide as a catalyst of choice in the reaction of PhMgBr with epoxyenone **63** and **64**, epoxyensulfone **65** and epoxyenamide **66** in Et_2O. Utilization of optimized catalytic procedure in the reaction of PhMgBr with epoxyenone **63** in Et_2O at lower temperature gave MIRC product **67e** in moderate yield and moderate diastereoselectivity (**Table 2.8**, entry 1). The reaction in the non-coordinating solvents (e.g., CH_2Cl_2, toluene) gave slightly better yields with better diastereoselectivity (entries 2 and 3, 68 vs 64%, dr 90:10 vs 92:8 respectively). Utilization of identical reaction conditions in the reaction of epoxy enone **64** with PhMgBr gave excellent yield and diastereoselectivity of MIRC product **68e** (entry 4, 88%, 100:0 dr). Epoxyensulfone **65** reacted with PhMgBr in the presence of catalytic amounts of zinc cyanide (0.1 equiv) affording good yields of MIRC product **69e** and **69e**' but with poor diastereoselectivity in Et_2O at room temperature (entry 5). The yield and diastereoselectivity was significantly increased while using CH_2Cl_2 or toluene as solvents (entries 6 and 7 respectively). The reaction of epoxyenamide **66** with PhMgBr in CH_2Cl_2 or toluene although gave moderate yield of MIRC products, the diastereoselectivity was quite poor (entries 8 and 9). In all of the tested reactions, biphenyl (3-14%) by-product was observed due to the competing coupling reactions of phenyl zincate reagents during or soon after the completion of MIRC reactions.

Table 2.8 $Zn(CN)_2$ Catalyzed MIRC Reaction of PhMgBr with Epoxides **63-66**.[82]



entry	epoxide	solvent	temp °C (h)	% yield[a] **A**	**B**	dr[b] (**A**:**B**)	% yield **60**[a]
1	**63**	Et_2O	-30 to rt (3)	63	-	88:12	11
2	**63**	CH_2Cl_2	-30 to rt (3)	68	-	90:10	9
3	**63**	PhMe	-30 to rt (3)	64	-	92:8	8
4	**64**	CH_2Cl_2	-20 to rt (4)	84	-	100:0	3
5	**65**	Et_2O	rt (4)	42	30	55:45	13
6	**65**	CH_2Cl_2	rt (4)	17	64	22:78	8
7	**65**	PhMe	rt (4)	5	82	7:93	7
8	**66**	CH_2Cl_2	rt (4)	62	-	22:78	14
9	**66**	PhMe	rt (4)	66	-	19:81	13

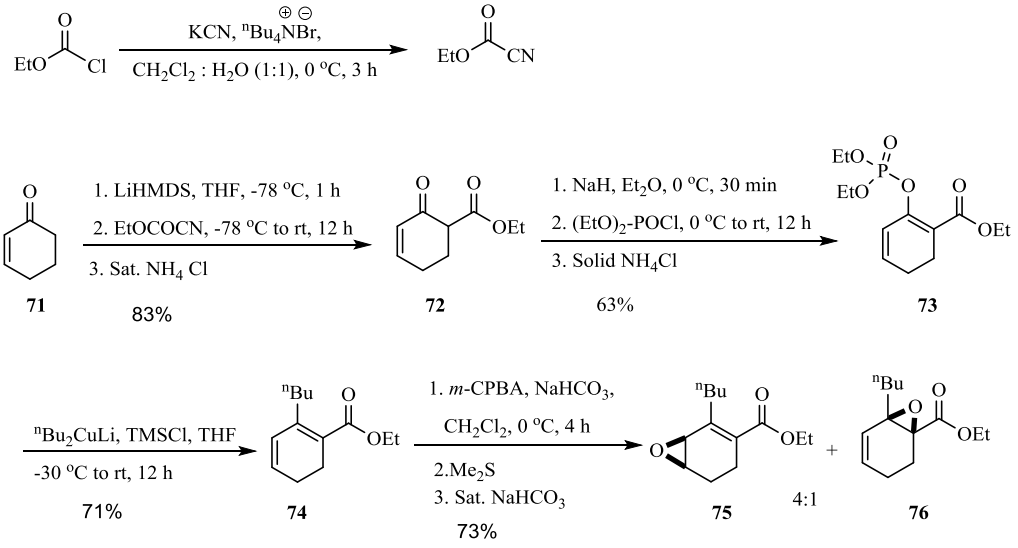
[a] Yields are based upon isolated products purified by column chromatography.
[b] Diastereomeric ratio was determined from the integration of ^1H NMR of the carbinol hydrogen absorption or via peak heights of the ^{13}C NMR absorption corresponding to the carbinol carbon.

2.55 Synthesis and Reactions of Cyclic Epoxyenoates

The great success in the MIRC reaction of Grignard reagents with acyclic functionalized epoxides in the presence of catalytic amounts of Zn(II) salts prompted us to extend the methodology with cyclic epoxyenoate. The requisite cyclic epoxyenoate **75** used for the reaction was synthesized by a slight modification of the literature procedures (**Scheme 2.24**).[109-114] The reaction of lithium enolate of 2-cyclohexenone with ethyl cyanoformate gave *β*-ketoenoate derivatives **72**, which on treatment with diethoxyphosphoryl chloride gave phosphate ester **73**. The phosphodieonate **73** was converted into **74** on reacting with lithium dibutylcuprate reagents. Epoxidation of **74** with *m*-CPBA in CH_2Cl_2 gave regioisomeric mixture of epoxide **75** and **76** (4:1) in good yields (73%).

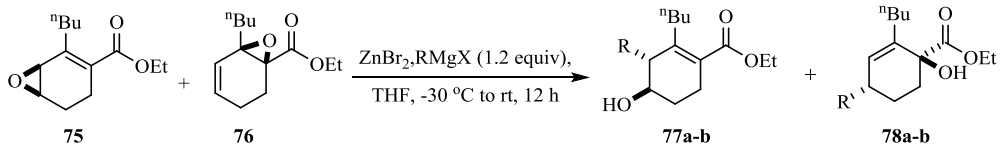
The column inseparable mixture of regioisomeric epoxides **75** and **76** was employed for the next step using procedure catalytic in $ZnBr_2$ (0.1 equiv).

Scheme 2.24 Synthesis of Cyclic Epoxide.



Unlike acyclic epoxides, the reaction of ^{n}BuMgCl (1.2 equiv) with the mixture of **75** and **76** in the presence of catalytic amounts of $ZnBr_2$ (0.1 equiv) in THF gave major S_N2 epoxide opening product **77a** probably resulting from epoxide **75** along with minor product **78a** probably resulting from **76**. Similarly, the reaction of ^{i}PrMgCl (1.2 equiv) with the mixture of **75** and **76** gave major **77b** and minor **78b** products (**Scheme 2.25**). The identity of these products was carried out using ^{1}H, ^{13}C-NMR, GC/MS and IR spectroscopic analyses. The lack of MIRC products in the reaction of cyclic epoxides with Grignard reagents in the presence of catalytic amounts of zinc bromide confined our investigation only to the acyclic epoxide hence further studies on cyclic system were abandon.

Scheme 2.25 $ZnBr_2$ Catalyzed Reaction of Grignard Reagents with Cyclic Epoxide.

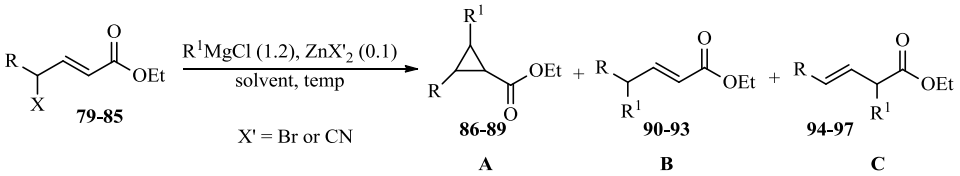


		77 (%)	78 (%)
a	R = ^{n}Bu	59	4
b	R = ^{i}Pr	57	5

2.56 MIRC Reactions of *γ*-Haloenoate

In pursuit of developing new and general methodology for the MIRC reaction, we briefly explored the susceptibility of organozincate reagents in the conjugate addition reactions with *γ,δ* -epoxyenoates, ketone, sulfone, and amide. Conjugate addition and cyclopropane formation was also observed when optimized catalytic procedure was employed for the *γ*-haloenoates. The reaction of ^{n}BuMgCl (1.2 equiv) with commercially available ethyl-4-bromocrotonate **79** in the presence of catalytic amounts of $ZnBr_2$ (0.1 equiv) gave good yields of MIRC product **86a** (**Table 2.9**, entry 1). Motivated from the preliminary results, a series of *γ*-alkyl-*γ*-haloenoates **80-84** were synthesized and employed for the MIRC reaction. Although the reaction of ^{n}BuMgCl with *γ*-bromoenoate **80** gave good yield of cyclopropanation product (entry 2), the reaction with *γ*-chloroenoate (entries 3-10) or *γ*-bromoenoate (entries 11-15) gave none to moderate yield of MIRC products. The reaction of ^{n}BuMgCl (1.2 equiv) with *γ*-chloroenoate **81** in THF despite consuming all starting materials, only moderate yields of cyclopropanation product was observed (entry 3-4). The application of TMSCl (2.0 equiv) actually lowered the yield of MIRC products (entry 5). ^{n}BuMgCl gave moderate yields of MIRC products in toluene at lower temperature (entry 6), while exclusive mixture of S_N2 and S_N2' substitution product was observed at higher temperature (entry 7). All starting material along with biphenyl byproduct (48%) was observed

Table 2.9 MIRC Reaction of *γ*-Haloenoates and *γ*-Selenoenoates.



79 R = H X = Br
80 R = Me X = Br
81 R = Et X = Cl
82 R = Et X = Br
83 R = Bn X = Cl
84 R = Bn X = Br
85 R = Et X = SePh

a R^1 = Bu
b R^1 = ^{i}Pr
c R^1 = Ph

86, 90, 94 R = H
87, 91, 95 R = Me
88, 92, 96 R = Et
89, 93, 97 R = Bn

entry	SM	R^1	ZnX_2'	solvent[a]	temp (^{o}C) (h)[b]	% conv.	% yield[c] **A**	**B:C** (% yield) [c]
1	**79**	^{n}Bu	$ZnBr_2$	THF	-78 to 25 (12)	100	62	-
2	**80**	^{n}Bu	$ZnBr_2$	THF	-78 to 25 (12)	100	63	-
3	**81**	^{n}Bu	$ZnBr_2$	THF	-78 to 25 (12)	50	43	-
4	**81**	^{n}Bu	$ZnBr_2$	THF	-78 (3)	100	72	-
5	**81**	^{n}Bu[d]	$ZnBr_2$	THF	-78 (3)	20	17	-
6	**81**	^{n}Bu	$ZnBr_2$	PhMe	-78 to 25 (12)	67	56	1:1 (18)
7	**81**	^{n}Bu	$ZnBr_2$	PhMe	0 to 25 (12)	100	-	1:1(75)
8	**81**	Ph[e]	$ZnBr_2$	PhMe	-78 (3)	0	-	-
9	**82**	^{n}Bu	$ZnBr_2$	THF	-78 to 25 (12)	100	-	3:2 (79)
10	**82**	^{n}Bu	$ZnBr_2$	CH_2Cl_2	-78 to 25 (12)	0	-	-
11	**82**	^{n}Bu	$ZnBr_2$	PhMe	-78 to 25 (12)	100	58	100:0 (12)
12	**82**	^{n}Bu	$Zn(CN)_2$	PhMe	-78 to 25 (12)	100	51[f]	2.2:1 (33)
13	**83**	^{n}Bu	$ZnBr_2$	THF	-78 to 25 (12)	50	37	-
14	**84**	^{n}Bu	$ZnBr_2$	THF	-78 to 25 (12)	0	-	-
15	**85**	^{n}Bu	$ZnBr_2$	THF	-78 to 25 (12)	-	-[g]	-

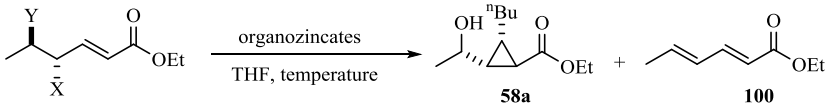
[a] Reactions were carried out at indicated solvents. [b] Percentage conversion was calculated from the GC/MS ratio of the crude product. [c] Yields are based upon isolated products purified by column chromatography. [d] TMSCl (2.0 equiv) was used for the reaction. [e] Biphenyl (48%) was observed in the reaction. [f] 6.5:1 dr at cyclopropane carbon bearing R-group. [g] PhSe^{n}Bu (53%) was isolated in the reaction but lost all starting materials.

when PhMgBr was reacted with **81** employing catalytic procedure (entry 8). To the contrary, the reaction of ^{n}BuMgCl with *γ*-bromoenoate **82** in THF gave the mixture of S_N2 and S_N2' substitution products (entry 9) while moderate yield of MIRC products along with minor S_N2 and S_N2' substitution products was observed in toluene (entry 10). The use of benzyl substituted *γ*-haloenoates **83** or **84** and *γ*-selenoenoate **85** failed to offer notable success in the MIRC reaction

(entry 11-15) in our preliminary investigations. The fine tuning of reaction conditions employing different solvents (e.g., coordinating or non-coordinating), zinc salts, temperatures and Lewis acids as additives can be used to enhance the yield and diasteroselectivity of cyclopropanation products in future. The stereochemistry of the products can be established by converting the MIRC products into cyrstalline derivatives followed by single crystal X-ray crystallography.

γ,δ -Disubstituted enoates containing γ-acetoxy or γ-halo leaving group (i.e., **98, 99A-B**) were less susceptible for the MIRC reaction with ^{n}BuMgCl under procedure catalytic in $ZnBr_2$ (**Table 2.10,** entries 1,5-6). These reactions gave cyclopropanation product **58a** in poor yields along with ethyl sorbet byproduct probably via the elimination of both γ- and δ -substituents. Utilization of $^{n}Bu_3ZnMgCl$ with **99A-B** (entry 2) or $^{n}Bu_3ZnLi$ with **98B** (entry 4) did not improve the yield of MIRC products.

Table 2.10 MIRC Reactions of Organozincates with γ,δ -Disubstitued Enoates.



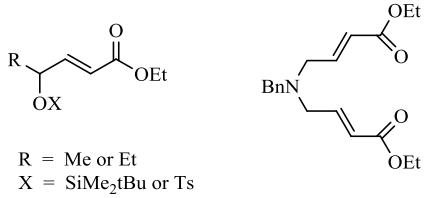
98 X = OAc Y = Br
99A X = Cl Y = OAc
99B X = Br Y = OAc

entry	SM[a]	reagents (equiv)	solvent	temp. (h)	GC ratio **sm:58a:100**[b]
1	**98**	^{n}BuMgCl (1.2), $ZnBr_2$ (0.1)	THF	-78 to rt (12)	90:5:5
2	**99A**	$^{n}Bu_3ZnMgCl$ (1.0)	THF	-78 to rt (12)	95:5:0
3	**99B**	$^{n}Bu_3ZnLi$ (1.2)[c]	THF	-78 to rt (12)	80:18:2
4	**99B**	$^{n}Bu_3ZnMgCl$	THF	-60 to rt (12)	50:30:20
5	**99B**	^{n}BuMgCl (1.2), $ZnBr_2$ (0.1)	THF	-40 to rt (12)	25:5:70
6	**99B**	^{n}BuMgCl (1.2), $ZnBr_2$ (0.1)	THF	-20 to rt (12)	50:25:25

[a] SM = starting materials. [b] Gas chromatography (GC) ratio was calculated from the integration of different peaks observed in the crude sample. [c] $Ni(acac)_2$ (0.1 equiv) was employed for the reaction.

No conjugate addition was observed in the reaction of Grignard reagents with *γ*-siloxy, *γ*-tosyloxy and *γ*-amino enoates using procedure catalytic in Zn(II) salts (**Scheme 2.26**).

Scheme 2.26 Unsuccessful Examples for the MIRC Reactions.

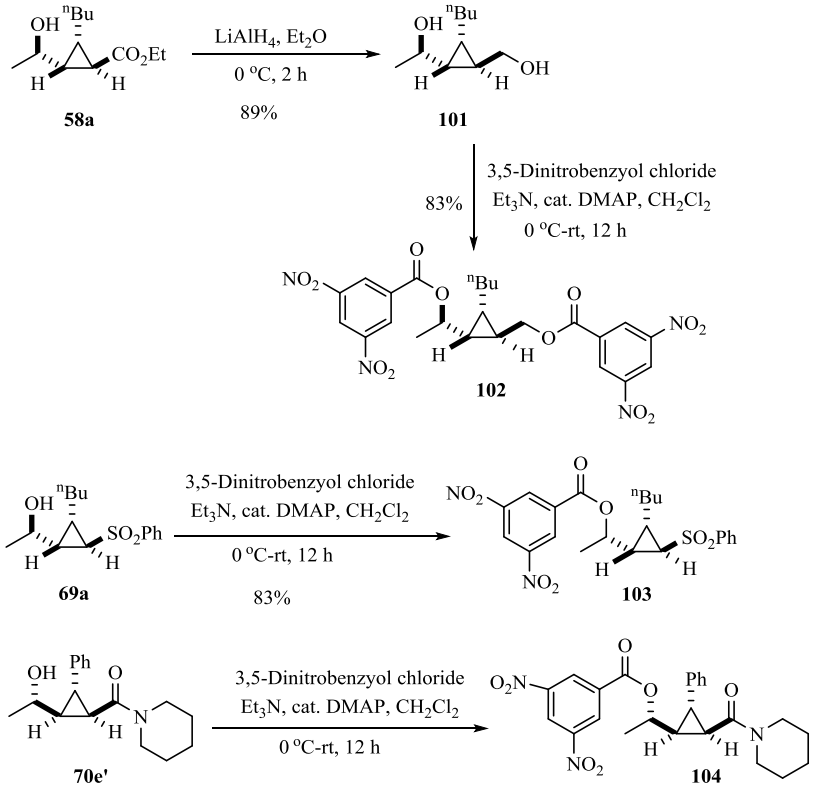


2.57 Stereochemical Assignment

The inability to convert the cyclopropyl ester **58a** into lactone **59a** in the presence of acid or base suggested the *trans*- disposition of the carbinol and carboalkoxy substituents. This tentative assignment was reinforced as lactone **59a** was an exclusive product while performing reaction in CH_2Cl_2 (**Table 2.1**, entry 10). The overlapping of all three ring hydrogens of 1,2,3-trisubstituted cyclopropane derivatives **58a-d, 58g** with alkyl substituent in ^1H NMR spectrum created problems for the determination of the stereochemistry of the MIRC products using conventional NOESY NMR. Hence, the relative stereochemistry of the products was determined by X-ray crystallographic study. The convertion of **58a** to 3,5-dinitrobenzoyl and napthanoyl derivatives did not offer good crystals while attempted syntheses of tosyl and nosyl derivatives of **58a** failed. The reduction of ester moiety into alcohol followed by synthesis of *bis*-3,5-dinitrobenzoyl derivatives **102** gave white needle shaped crystals in acetone. The X-ray analysis of crystal showed *n*-butyl group and 1-(3,5-dinitrobenzoyloxy)-ethyl groups are *cis* to each other while both groups are *trans* to the ester bearing 3,5-dinitrobenzoyloxy methyl group as shown in **Scheme 2.27**.

The major diastereomer of 1,2,3-trisubstituted cyclopropyl sulfone **69a** in the THF was converted into the corresponding 3,5-dinitrobenzoyl derivatives **103** that crystalized out from saturated acetone solution. The minor 1,2,3-trisubstituted cyclopropyl sulfone **69a'** gave crystals in Et_2O. The stereochemistry of both of these crystals was determined using single crystal X-ray crystallography. The X-ray study of the major isomer **69a** showed *n*-butyl group and 1-hydroxyethyl group *cis* to each other while both groups are *trans* to the sulfone substituent. The minor isomer **69a'** had *n*-butyl group *trans* to both the 1-(3,5-dinitrobenzoyloxy)-ethyl and the sulfone substituent.

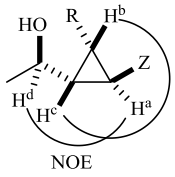
Scheme 2.27 Stereochemical Assignments of Cyclopropylester **58a** Cyclopropylsulfone **69a** and Cyclopropyl Amide **70e'**.



The stereochemistry of substituted cyclopropyl amide **70** was also determined by X-ray crystallography. The minor cyclopropyl amide **70e** gets crystallized out from the CH_2Cl_2 solution

and their single crystal X-ray analysis confirmed that phenyl substituent in cyclopropane ring is *cis* to 1-hydroxyethyl substituents however both of these groups are *trans* to amide substituents. On the other hand, conversion of the major isomer **70e**' into corresponding 3,5-dinitrobenzoyl derivative **104** followed by X-ray crystallography of the crystal showed phenyl substituent in cyclopropane ring is *trans* to both amide substituents and 1-(3,5-dinitrobenzoyloxy)-ethyl substituents. 50% Probability thermal ellipsoids for all these crystals are reported in **Figure 2.2-2.6.** Crystal data and structural refinement for corresspodning crystals are reported in **Table 2.11-2.15** and crystallographic informations (CIF) files are reported in the appendix A.

In order to determine the relative stereochemistry of the cyclopropyl ketones, NOESY NMR of ketones **67e** and **68e** was taken and compared with the corressponding spectra of ester **58d**. The presence of the phenyl substitutent in cyclopropyl ester **58d** and cyclopropyl ketone **67e** and **68e** dispersed the absoptions peaks of cyclopropyl hydrogens in ^{1}H NMR. The H^a, H^b, H^c and H^d proton assignments for **58d**, **67e** and **68e** were determined from COSY NMR. In the NOESY spectra of these compounds, strong coupling between H^a and H^d and H^b and H^c and weak coupling between H^a and H^b, H^a and H^c a nd H^c and H^d was observed confirming the assigned stereochemistry. These experiment confirmed that both alkyl and aryl Grignard reagents gave same relative stereochemistry about the cyclopropane ring on reaction with epoxy enones and enoates.



58d Z = CO_2Et, R = Ph
67e Z = PhCO, R = Et, Ph
68e Z = ^{i}PrCO, R = Ph

2.6 Discussion

The stereochemistry of the MIRC products observed in the reaction of Grignard reagents with epoxyenoates **55**, epoxyenones **63-64**, epoxyensulfones **65** and epoxyenamides **66** in the presence of catalytic amounts of zinc bromide can be rationalized by solvation model as shown in **Scheme 2.28**. Intriguingly, **55** gave major diastereomer **58a** in THF and only lactone **59a** in CH_2Cl_2 with $^nBu_3ZnLi$ in the presence of catalytic amounts of $ZnBr_2$ (**Table 2.1**). A plausible rationalization of this result involved minimization of $A^{1,3}$-strain in the *trans*ition state structures arising from conformers **105-107** where the stability of the conformers was expected in the order of **105>107>106**. The solvent dependent nature of the zincate reagent involving solvent separated ion pairs (SSIP) in coordinating solvents (e.g., THF or Et_2O) and contact ion pairs (CIP) in non-coordinating solvent (e.g., CH_2Cl_2, toluene) further supports the proposed model. Recent X-ray crystal structures and solution NMR studies have elucidated the formation of mixed bimetallic complexes upon mixing Grignard reagents with ZnX_2 (X = Cl, Br) or ZnR_2 compounds in THF[115, 116] and have implicated $[(THF)_6Mg(\eta\text{-}Cl)_3]^+$ $[Zn_2Et_5]^-$ in $ZnCl_2$ mediated addition of EtMgCl to benzophenone.[116] The structures of these mixed Mg-Zn complexes is dependent upon the alkyl ligand (e.g., ^{t}Bu vs. Et)[115, 116] and are in dynamic equilibrium with a variety of zinc species depending upon concentration.[115] The composition and structures of mixed Mg-Zn complexes in solvents other than THF are unknown but if similar to those shown in **Figure 2.1**, it would be reasonable to expect SSIP in THF and tight CIP in toluene and CH_2Cl_2.

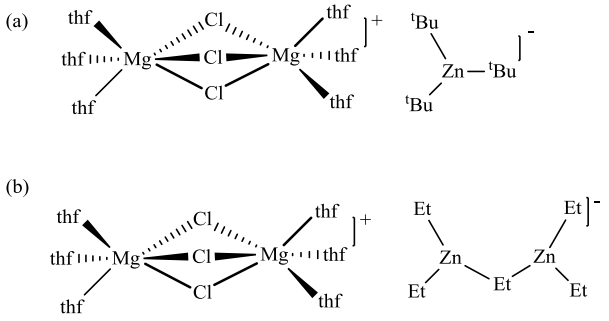
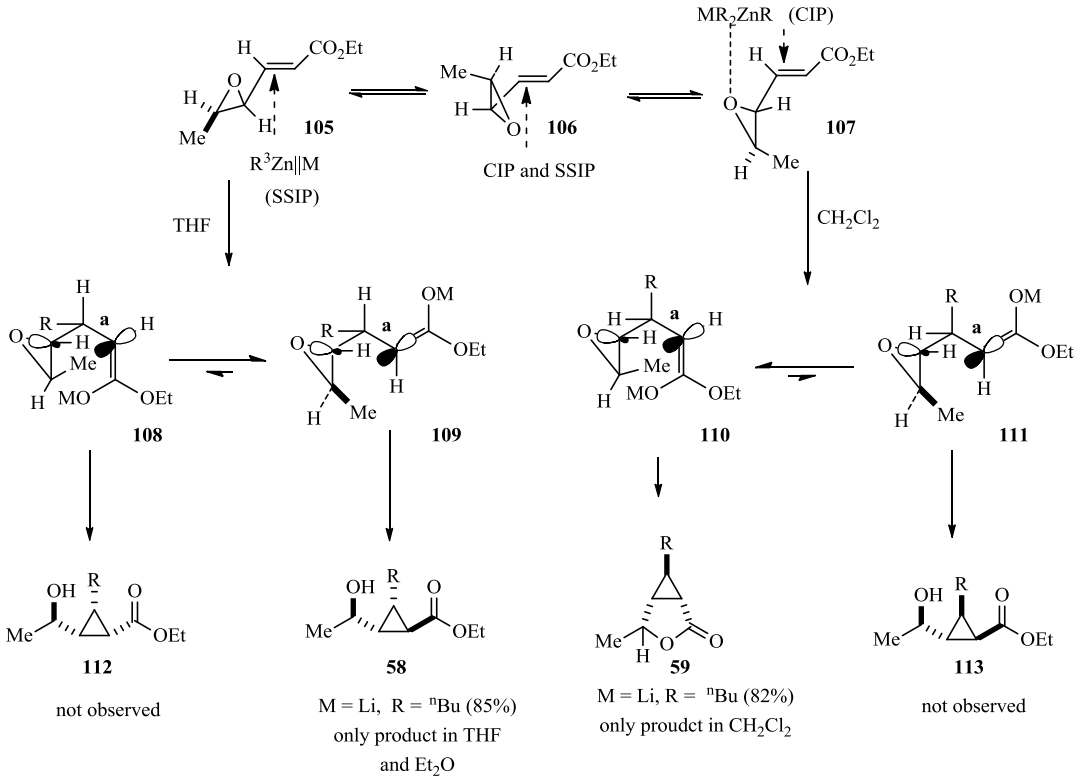


Figure 2.1. Mixted Bimetallic Zn-Mg Complexes (a) $[\{Mg_2Cl_3(THF)_6\}^+\{Zn(^tBu)_3\}^-]$ in the Reaction of ^{t}BuMgCl (3.0 equiv) with $ZnCl_2$ (1.0 equiv) in THF and (b) $[\{Mg_2Cl_3(THF)_6\}^+\{Zn_2Et_5\}^-]$ in the Reaction of EtMgCl (3.0 equiv) with $ZnCl_2$ (1.0 equiv) in THF. [Reprinted with permission from *J. Org. Chem.* **2013**, *78*, 12426-12439. Copyright (2013), American Chemical Society].[82]

Due to electrostatic dipole-dipole repulsion, the SSIP approaches the alkene π-face from the side opposite the polar heteroatom substituent (i.e., the epoxide in **105**) to give conformers **108** and/or **109**; while the CIP approaches from the alkene π-face from the same side perhaps enhanced by complexation with the magnesium counter-ion (i.e., **107**) give conformers **110** and/or **111**. Conformers **108-109** and **110-111** can arise directly from the conjugate addition process or by C-C bond rotation prior to cyclopropane formation. The initial formation of configurational diastereomers arising from zincate attacks on the enoate either syn or anti to the epoxide determines the stereochemical outcome during cyclopropane formation. Zincate attack anti to the epoxide leads to conformational diasteromers **108** and **109** with proper orientation to afford cyclopropanes **112** and **58b**, respectively. In conformer **108** the R-group and the enolate are eclipsed about bond **a**, while in conformer **109** they are oriented anti and this anticipated lower energy conformer in the *trans*tition state leads to the observed product **58b**. Similarly, in the *trans*ition states corresponding to conformers **110** and **111** arising from zincate syn attack, conformer **110** has the R-enolate eclipsed arrangement about bond **a**, while **111** has the lower energy anti arrangement leading to the observed product **59b**. This analysis implies that the R-

group (from the zincate reagent) and the EWG will always be *trans* to each other. Previous rationalizations invoking a carbanionic lithium enolate seem unlikely given computational studies on enolate anions.

Scheme 2.28 Possible Reaction Pathways in the Addition of Lithium/Magnesium Trialkylzincate to Michael Substrate.[82]



If the solvent affects the syn:anti ratio (i.e., the initial 1,4-addition occurring syn or anti to the epoxide), why is there no solvent effect for the epoxyenones, clean reversal of diastereoselectivity for the epoxyenoates, and poor (in THF) to modest to excellent (in CH_2Cl_2) distereoselectivity for the epoxy ensulfones and enamides? To probe this question, we performed several competition experiments with one equivalent of Grignard reagent and one equivalent each of two electrophiles. Treatment of 1.0 equivalents of enone **64** and enoate **55** with ^{n}BuMgCl [CH_2Cl_2 or THF, $ZnBr_2$ (0.1 equiv), -40 to 25 ^{o}C, 12 h)] gave complete conversion of **64** to **68c**

with complete recovery of **55**, while reaction of **55** and **65** under the same condition in CH_2Cl_2 gave a 35:65 ratio recovered **55:65** along with the cyclopropanes **59b** and **69c**. Similarly, reaction of **65** and **66** gave a 73% recovery of **65** and 27% of **66**. These competition experiments establish that the relative rate factors for reaction of **65**:**55**:**66** are 10:2:7.2:1 in CH_2Cl_2.

The relative basicities of the EWGs (i.e., pK_{BH^+}) in **55** and **63-66** can be estimated from reported values for similar compounds where $PhSO_2Ph$ (-12.37) < $MeSO_2Me$ (-12.27) < RCOR (-7) < RCO_2R (-6.5) < ROR (-3.5) < THF (-2.05) < $RCONH_2$ [$pK_{BH^+}(O)$ = -0.5] in basicity.[117] Similarly, the relative electron withdrawing power of the carbonyl and sulfonyl groups can be estimated from Hammett σ_R^+-substitutent constants decreasing in power with –COMe (0.16) ≈ -CO_2Me (0.16) > -SO_2Me (0.12) > -$CONH_2$ (0.00).[118] Although these parameters specifically measure proton acceptor and donor properties (i.e., the acidity of substituted benzoic acid), they should qualitatively reflect magnesium complexation and Michael acceptor susceptibility. From this analysis the sulfone, ketone, and ester are less basic than the epoxide, while the σ_R^+ substitutent constants correlate with the relative rates measured by competition experiments with **64**>**55**>**65** but not with **66**, with **66**>**55**>**65** in reactivity. Thus, the most reactive epoxy ketones **63-64** show no solvent dependent diastereoselectivity, while the less reactive ester **55** and sulfone **65** substates do, with the more reactive ester giving excellent but different diastereoselectivity in THF and CH_2Cl_2. The least reactive epoxy sulfone **65** is also the least basic, the second poorest Michael acceptor and shows excellent diastereoselectivity in CH_2Cl_2 and poor diastereoselectivity in THF. Epoxy amide **66** is expected to be the poorest Michael acceptor based upon Hammett σ_R-substitutent constants but is the most basic substrate and its relative reactivity (i.e., **66** > **55** > **65**) suggests amide-magnesium ion complexation is facilitating the conjugate addition reaction. The correlation of reactivity with diastereoselectivity is clearly seen in the reactions of PhMgCl with epoxy ester **55** (Table 2.7, entries 11-14) where the less reactive putative phenylzincates give

poor diastereoselective at -20 to 0 ^{o}C and better diastereoselectivity at 25 ^{o}C that is in turn lower than those obtained with the more reactive alkylzincate reagents (**Tables 2.1, 2.2** and **2.5**).

Although the details remain to be elucidated, the observed solvent dependent diastereoselectivity of the epoxy ketones, ester, sulfone and amide appears to reflect a complex interplay between functional group basicity and electron withdrawing capacity. Thus, the more reactive epoxyketones **63**-**64** show no solvent dependence, while the least reactive epoxyamide **66** never gives a single diastereomer under any reaction conditions. The epoxyester **55** and sulfone **65** display intermediate behavior.

As a proof of concept, MIRC reactions of organozincate reagents with γ-haloenoates gave poor to moderate yields of cyclopropanation products. Utilization of γ-acetoxy-δ -halo or γ-halo-δ -acetoxy enoates however gave cyclopropanation products in poor yield even under optimized reaction conditions. No conjugate addition was observed for γ-siloxy, γ-tosyloxy and γ-amino substrates. Although a linear correlation was not found, our McSpartan calculations suggested that LUMO energies might play a role. Silyl substituents are particularly intriguing since the C-Si bonding orbital stabilizes adjacent carbocations and is expected to lower the LUMO energies for these electron deficient alkenes. It is likely that ring strain in the γ,δ-epoxide might also play a role for the feasibility of the reaction with functionalized vinyl substrates.

2.7 Conclusion

In summary, we successfully established a new methodology for the addition of organozincate reagents generated either stoichiometrically or catalytically to selected *γ,δ*-epoxy-*α,β*-enoates, **63** and **64**, ensulfone **65** and enamide **66** and to *γ*-halo-*α,β*-enoates followed by intramolecular cyclization to generate cyclopropyl derivatives with excellent stereochemical control. In some instances, two different stereiosomers were obtained as single products simply by changing the solvent providing a convenient procedure for stereo divergent control. Although, the attempted MIRC reaction of triaryl or alkylarylzincate reagents with epoxides **55**, **63-66** failed, the modification of procedure using reverse addition of aryl Grignard reagents in the presence of catalytic amounts of zinc (II) salts gave desired products in good yield and good diastereoselectivity. These novel applications of zinc reagents, which normally undergo 1,4-additions to cyclic sterically unhindered ketones, provide opportunities to develop Michael Initiated Ring Closing (MIRC) reactions that provide synthetic routes to a range of substituted cyclopropanes (e.g., aryl, phosphate, 2-amino-1-carboxylates, trifluromethyl, vinyl). Despite these achievements, the reaction of organozincates with epoxynitro compound **71** gave 1,4-adduct while the reaction with cyclic epoxide **77** under identical conditions gave S_N2 epoxide opening products while attempted MIRC reaction of Grignard reagents with *γ*-haloenoates or *γ*-selenoenoates **79-85** gave low yields of cyclopropanation products. Perhaps, a through investigation for the optimized conditions by varying solvents or temperature would shed additional light on the mechanism governing the cyclopropanation methodology described herein.

2.8 Future Directions

Although the methodology discussed above was successful for the MIRC reaction of Me-, Et-, ^{n}Bu-, ^{i}Pr- and Ph- Grignard reagents with substrates **55, 63-66, 71** and **77** in the presence of catalytic amounts of zinc(II) salts, we failed to extend the protocol to other aryl and heteroaryl zincate reagents. The fine tuning of reaction conditions for the diastereoselective cyclopropanation reaction of in situ generated aryl and heteroaryl zincates with these substrates will be investigated in our laboratory. The substrate controlled enantioselective cyclopropanation reaction of chiral epoxides with Grignard reagents using procedure catalytic in zinc (II) salt and/or using chiral Zn(II) reagent for the enantioselective cyclopropanation products will be the next area of interest in our laboratory. The successful developments of these procedure varying reactions conditions (e.g., solvents, temperature, catalytic amounts of additives) will significantly extend the scope of MIRC reaction in future.

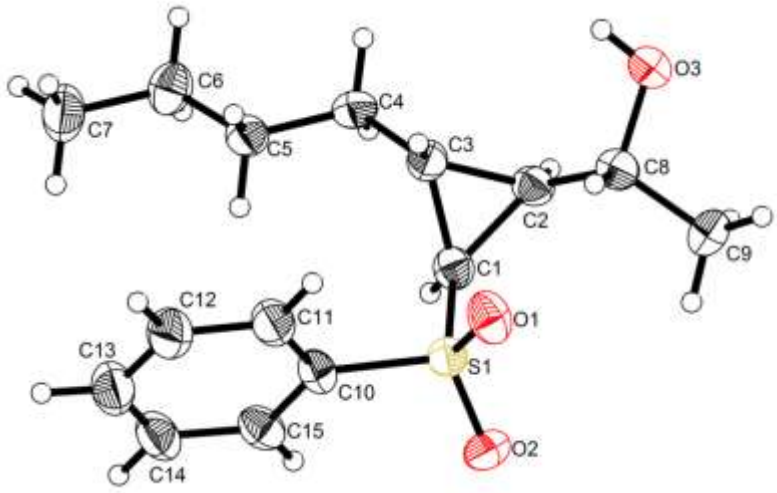


Figure 2.2 50% Probability Thermal Ellipsoids of **69a**.

Table 2.11 Crystal Data and Structural Refinement for **69a**.

Empirical formula	$C_{15}H_{22}O_3S$	
Formula weight	282.39	
Temperature	178 K	
Wavelength	0.71073Å	
Crystal system	Orthorhombic	
SG	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.6271 (16) Å	$\alpha = 90^{o}$
	b = 13.257 (4) Å	$\beta = 90^{o}$
	c = 20.571 (9) Å	$\gamma = 90^{o}$
Volume	1534.6 (8) $Å^3$	
Z, calculated density	4, 1.222 Mg/m^3	
Absorption coefficient	0.213 mm^{-1}	
F (000)	608	
Crystal size	0.70 x 0.05 x 0.05 mm	
Theta range for data	3.07 to 26.38 degree	
Index ranges	-7<=h<=6, -16<=k<=15, -25<=l<=25	
Reflns col./unique	12308 / 3128 [R(int) = 0.0836]	
Completeness	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. *trans*mission	0.9894 and 0.8654	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3128 / 0 / 175	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2siga (I)]	R1 = 0.0582, wR2 = 0.1419	
R indices (all data)	R1 = 0.0792, wR2 = 0.1600	
Absolute structure parameter	0.44(14)	
Largest diff. peak and hole	0.394 and -0.385 $e.A^{-3}$	

CIF file for compound **69a** is attached in the appendix A.

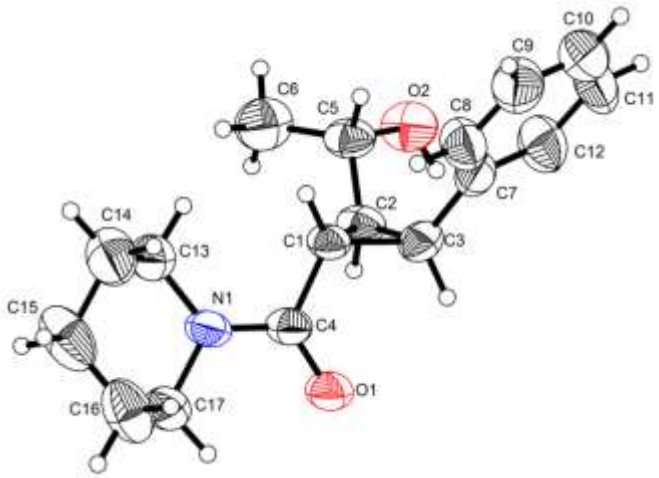


Figure 2.3 50% Probability Thermal Ellipsoids of **70e**.

Table 2.12 Crystal Data and Structural Refinement for **70e**.

Empirical formula	$C_{17}\,H_{23}\,N\,O_2$	
Formula weight	273.36	
Temperature	203 K	
Wavelength	0.71073Å	
Crystal system	Monoclinic	
SG	P2(1)/c	
Unit cell dimensions	a = 20.875 (4) Å	α = 90 ^{o}
	b = 14.302 (4) Å	β = 102.85(3) ^{o}
	c = 10.553 (2) Å	γ = 90^o
Volume	3071.7 (10) Å^3	
Z, calculated density	8, 1.182 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F (000)	1184.0	
Crystal size	0.70 x 0.12 x 0.12 mm	
Theta range for data	2.43 to 26.81 deg.	
Limiting Indices	-25<=h<=25, -17<=k<=17, -11<=l<=12	
Reflections collected/unique	25248 / 5564 [R (int) = 0.1779]	
Completeness	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. *trans*mission	0.991 and 0.989	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5564 / 0 / 363	
Goodness-of-fit on F^2	1.244	
Final R indices[I>2siga (I)]	R1 = 0.1197, wR2 = 0.2033	
R indices (all data)	R1 = 0.2334, wR2 = 0.2610	

CIF file for compound **70e** is attached in the appendix A.

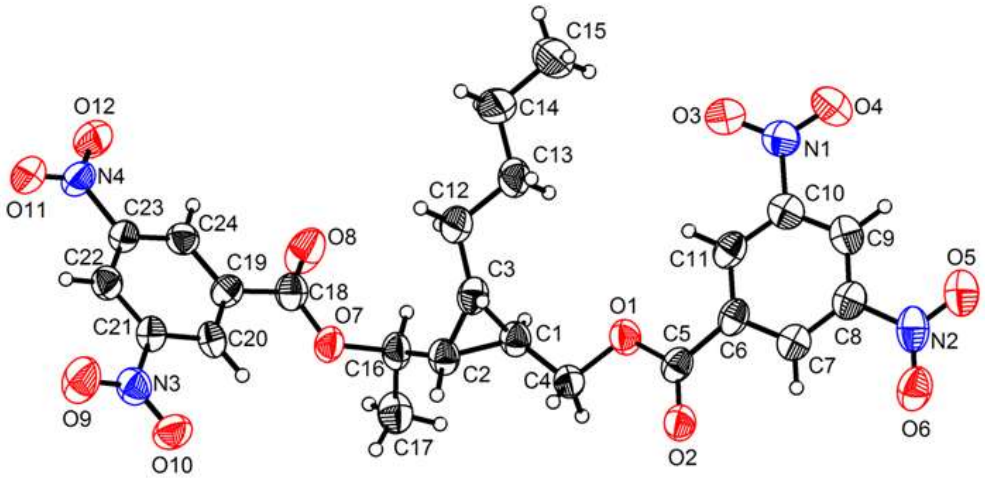


Figure 2.4 50% Probability Thermal Ellipsoids of **102.**

Table 2.13 Crystal Data and Structural Refinement for **102**.

Audit creation method	shelxl	
Empirical formula	$C_{24}H_{24}N_4O_{12}$	
Formula weight	560.47	
Temperature	188 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
SG	C2/c	
Unit cell dimensions	a = 27.518 (8) Å	α = 90 ^{o}
	b = 6.7633 (13) Å	β = 94.103 (7)^o
	c = 30.912 (7) Å	γ = 90^o
Volume	5738 (2) Å^3	
Z, calculated density	8, 1.297 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	
F (000)	2336	
Crystal size	0.60 x 0.22 x 0.02	
Theta range for data	2.94 to 25.03 deg	
Index ranges	32<=h<=32, -8<=k<=8, -32<=l<=36	
Reflns col./unique	19088 / 5043 [R(int) = 0.1125]	
Completeness	99.7 %	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5043 / 0 / 363	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2siga (I)]	R1 = 0.1071, wR2 = 0.2764	
R indices (all data)	R1 = 0.1621, wR2 = 0.3373	
Largest diff. peak and hole	0.475 and -0.419 e.A^{-3}	

CIF file for compound **102** is attached in the appendix A.

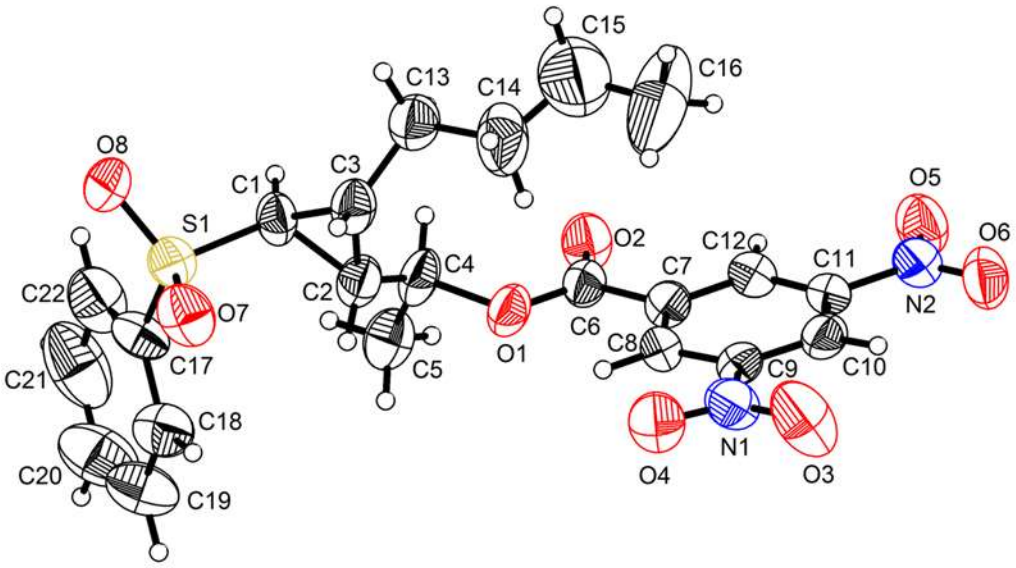


Figure 2.5 50% Probability Thermal Ellipsoids of **103**.

Table 2.14 Crystal Data and Structural Refinement for **103**.

Empirical formula	$C_{22}H_{24}N_2O_8S$	
Formula weight	476.49	
Temperature	183 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
SG	P1	
Unit cell dimensions	a = 10.6535 (18) Å	α = 73.751 (19) ^{o}
	b = 12.7422 (18) Å	β = 75.66 (2) ^{o}
	c = 19.093 (2) Å	γ = 85.64 (2)^o
Volume	2410.8 (6) $Å^3$	
Z, calculated density	4, 1.313 Mg/m^3	
Absorption coefficient	0.182 mm^{-1}	
Crystal size	0.38 x 0.19 x 0.06 mm	
Theta range for data	2.03 to 25.03 deg.	
Index ranges	-12<=h<=12, -15<=k<=15, -21<=l<=22	
Reflns col./unique	16769 / 8404 [R (int) = 0.1565]	
Completeness	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. *trans*mission	0.9891 and 0.9339	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	8404 / 0 / 599	
Goodness-of-fit on F^2	1.168	
Final R indices[I>2siga (I)]	R1 = 0.1445, wR2 = 0.2687	
R indices (all data)	R1 = 0.2722, wR2 = 0.3560	
Largest diff. peak and hole	0.656 and -0.495 $e.A^{-3}$	

CIF file for compound **103** is attached in the appendix A.

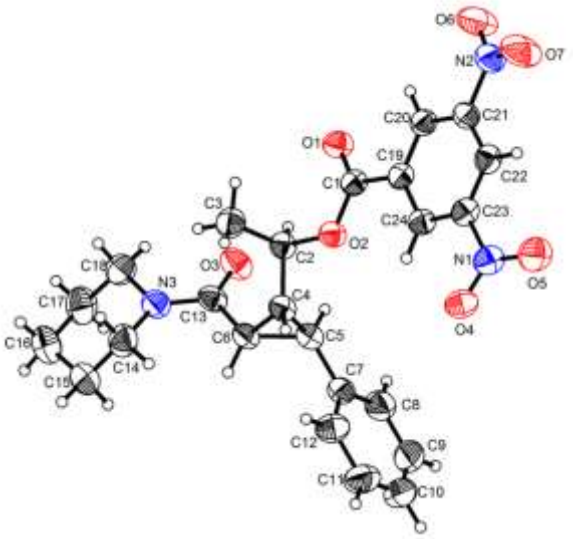


Figure 2.6 50% Probability Thermal Ellipsoids of **104**.

Table 2.15 Crystal Data and Structural Refinement for **104**

Audit creation method	shelxl	
Empirical formula	$C_{24}\ H_{25}\ N_3\ O_7$	
Formula weight	467.47	
Temperature	203 K	
Wavelength	0.71073Å	
Crystal system	Monoclinic	
SG	P2(1)/c	
Unit cell dimensions	a = 13.755 (3) Å	α = 90 ^{o}
	b = 16.362 (3)Å	β = 104.44 (3) ^{o}
	c = 10.483 (2) Å	γ = 90^o
Volume	2284.7 (8) Å^3	
Z, calculated density	4, 1.359 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F (000)	984.0	
Crystal size	0.44 x 0.36 x 0.33 mm	
Theta range for data	2.5 to 26.4 deg.	
Limiting indices	16<=h<=17, -20<=k<=20, -13<=l<=11	
Reflections collected / unique	17599 / 4031 [R(int) = 0.0535]	
Completeness	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. *trans*mission	0.957 and 0.967	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4644 / 0 / 308	
Goodness-of-fit on F^2	1.033	
Final R indices[I>2siga (I)]	R1 = 0.0662, wR2 = 0.1692	
R indices (all data)	R1 = 0.0862, wR2 = 0.1930	
Largest diff. peak and hole	0.25 and -0.25 e.A^{-3}	

CIF file for compound **104** is attached in the appendix A.

2.9 Experimental

Some of the experimental procedures and IR, GC/MS and NMR data used in this chapter were recently published[82] and reported here with the permission from American Chemical Society.

General. NMR spectra were recorded as $CDCl_3$ or C_6D_6 solutions on a 300 or 500 MHz NMR instrument. The ^1H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0.00) or $CHCl_3$ (δ = 7.28) or C_6H_6 (δ = 7.16) as internal standard. The ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to the $CDCl_3$ signal (triplet, centerline δ = 77.0 ppm) or C_6D_6 signal (multiplet, centerline δ = 128.4 ppm). Infrared (IR) spectra were recorded as neat samples (liquid films on NaCl plates). Gas chromatography-mass spectrometry measurements were performed on a GC coupled to a quadrupole detector at 70 eV. Analytical thin layer chromatography (TLC) was performed on silica gel plates, 200 μ mesh with F254 indicator. Visualization was accomplished by UV light (254 nm), and/or a 10 % ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 230-400 mess silica. The yields are of materials isolated by column chromatography.

Materials. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were distilled from sodium benzophenone ketyl. Toluene was dried over molecular sieves and used for the reactions. ^{n}BuLi (2.5 M in hexane), MeLi (1.6 M in Et_2O), and ^{t}BuLi (1.7 M in pentane) were commercially available and were titrated using *sec*-butyl alcohol and 1,10-phenanthroline monohydrate in THF. ^{n}BuMgCl (2.50 M in THF), ^{n}BuMgCl (1.7 M in THF), EtMgCl (2.0 M in Et_2O), MeMgCl (3.0 M in Et_2O), ^{i}PrMgBr (2.0 M in Et_2O), ^{t}BuMgCl (1.7 M in THF) and PhMgBr (2.80 M in Et_2O) were commercially available and titrated using menthol and 1,10-phenanthroline monohydrate in THF.[119] Zincate reagents were synthesized from

corresponding lithium or magnesium reagents and dried Zn(II) salts. All glasswares were flamed-dried under high vacuum and purged with argon and then cooled under a dry nitrogen atmosphere. Low temperature baths (up to -78 ^{o}C) were prepared using thermoflasks using dry ice-*iso*-propanol slush bath mixtures or ice-NaCl (-23 ^{o}C) mixture. All reactions were conducted under a positive, dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

HRMS data on compounds **58a', 58e, 58g, 59e, 67a-e, 68e, 69c', 69d', 69f, 69f', 70a, 70a', 70e** and **70e'** were analyzed with a Q-TOF detector (hybrid quadrupole time of flight MS). Compounds **55, 59a, 56a, 56c, 56d, 57a**, **57c, 63**, **66, 74**, **81**, **82**, **86** and **92** have been fully characterized and reported.[39, 103, 105, 110, 112, 120-126]

General Procedure A: Reaction of lithium trialkylzincate (R_3ZnLi) with ethyl *γ,δ*-epoxy-*α,β*-hexenoate (55). To an ice cold solution of flame dried $ZnBr_2$ (225 mg, 1.0 mmol) in THF (4.0 mL) under argon was added alkyllithium (3.0 mmol) and the reaction mixture was stirred for 30 minutes at 0 ^{o}C. Ethyl *γ,δ*-epoxy-*α,β*-hexenoate (156 mg, 1.0 mmol) was added and the resulting mixture was stirred for 2-12 hours at the indicated temperature. The reaction was quenched with NH_4Cl-NH_4OH aqueous buffer (pH = 7.0, 10.0 mL), filtered and the filtrate was extracted with Et_2O (3 x 15.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10-20% EtOAc in petroleum ether, v/v) to give pure compounds.

General Procedure B: Reaction of mixed lithium organozincates ($R^1R^2R^3ZnLi$) with ethyl *γ,δ*-epoxy-*α,β*-hexenoate (55). To an ice cold solution of flame dried $ZnBr_2$ (225 mg, 1.0 mmol) in THF (4.0 mL) under argon was added R^1Li (1.0 mmol), R^2Li (1.0 mmol) and R^3Li (1.0 mmol) and the mixture was stirred for 30 min at 0 ^{o}C. The flask was then *trans*ferred to -20 ^{o}C bath,

ethyl γ,δ -epoxy-α,β-hexenoate (156 mg, 1.0 mmol) was added and the mixture was stirred for the indicated time. The reaction mixture was quenched with NH_4Cl-NH_4OH aqueous buffer (pH = 7.0, 10.0 mL), filtered and the filtrate was extracted with Et_2O (3 x 15.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10-20% EtOAc in petroleum ether, v/v) to give pure compounds.

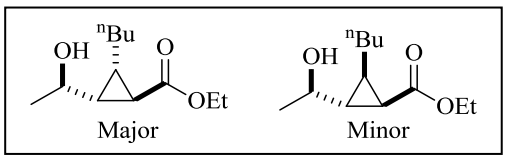
General Procedure C: Reaction of alkyl Grignard reagents with ethyl γ,δ-epoxy-α,β-unsaturated esters 55, ketones 63-64, sulfones 65 and amides 66 in the presence of catalytic amounts of zinc bromide. To an ice cold solution of flame dried $ZnBr_2$ (23 mg, 0.1 mmol) in THF or Et_2O or CH_2Cl_2 or toluene (4.0 mL) under argon was added the Grignard reagent (1.2 mmol) and the mixtures was stirred for 5 min at 0 ^oC. The flask was then cooled in a -20 to -30 ^oC bath, epoxide (1.0 mmol) was added and the mixture was stirred for 2-12 hours with gradual warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl, filtered and the filtrate was extracted with Et_2O (3 x 15.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography(silica, 10-20% EtOAc in petroleum ether, v/v) to give pure compounds.

General Procedure D for Reverse Addition: Reaction of phenylmagnesium bromide with ethyl 4,5-epoxy-2,3-unsaturated ester 55, ketone 63-64, sulfone 65 and amide 66 in the presence of catalytic amounts of zinc (II) salt. To an ice cold solution of dried Zn(II) salts (0.1 mmol) in Et_2O or CH_2Cl_2 or toluene (4.0 mL) under argon was added epoxide (1.0 mmol) and then the phenylmagnesium bromide (1.2 mmol) was added and the mixture was stirred for indicated hours at given temperature range. The reaction mixture was quenched with saturated

aqueous NH_4Cl, filtered and the filtrate was extracted with Et_2O (3 x 15.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10-20% EtOAc in petroleum ether, v/v) to give pure compounds.

General Procedure E for Competition Experiments: Reaction of Grignard reagents (1.0 equiv) with a 1:1 mixture of ethyl *γ,δ*-epoxy-*α,β*-unsaturated ester 55 (1.0 equiv) and other epoxides (1.0 equiv) such as *γ,δ*-epoxy-*α,β*-unsaturated ketone 64, *γ,δ*-epoxy-*α,β*-unsaturated sulfone 65 and 1:1 mixture of ethyl *γ,δ*-epoxy-*α,β*-unsaturated sulfone 65 (1.0 equiv) with *γ,δ*-epoxy-*α,β*-unsaturated amide 66 (1.0 equiv) in the presence of catalytic amounts of $ZnBr_2$. To the flame dried solution of $ZnBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 (4.0 mL) under argon was added $^{n}BuMgCl$ (1.0 mmol) at -40 ^{o}C. To this solution was added the 1:1 mixture of two epoxides under study in CH_2Cl_2 (2.0 mL) and reaction mixture was allowed to wam up to room temperature over 12 hrs. The reaction was quenched with saturated aqueous NH_4Cl, filtered and the filtrate was extracted with CH_2Cl_2 (3 x 15.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo. The crude product was subjected to NMR and GC/MS analysis and the ratio of each component were calculated from corresponding data.

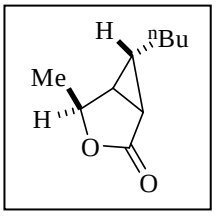
(1R*,2R*,3S*,1'R*) Ethyl 2-(1-hydroxyethyl)-3-butyl cyclopropane carboxylate (58a).



Employing general procedure A and using $^{n}BuLi$ (1.2 mL, 2.5 M in hexane, 3.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl *γ,δ*-epoxy-*α,β*-hexanoate (156 mg, 1.0 mmol) gave after purification by flash column chromatography (silica, 10-20 % EtOAc:petroleum ether, v/v) **58a** and **58a'** (177 mg, 82 %, dr 96:4) as a colorless

oil (the application of General procedure C gave 182 mg, 85%, 100:0 dr). **Major (58a)**: IR (neat) 3457 (br s), 2961 (s), 2932 (s), 1724 (s), 1450 (s), 1374 (s), 1176 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 4.6 Hz, 1H), 1.26 (t, J = 6.8 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.35-1.39 (m, 2H), 1.42-1.45 (m, 4H), 1.59-1.71 (m, 2H), 2.01 (s, 1H), 3.52 (dq, J = 3.2, 9.6 Hz, 1H), 4.13 (q, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 22.4, 23.4, 25.1, 27.0, 27.6, 31.8, 34.4, 60.4, 67.0, 173.7; mass spectrum *m/z* (relative intensity) EI 214 (0.04, M^+), 196 (2), 169 (100), 157 (43), 141 (12), 128 (52), 123 (15), 99 (59), 81 (66), 55 (59). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35 %; found: C, 67.63; H, 10.59 %. **Minor (58a'):** IR (neat) 3457 (br s), 2956 (s), 2932 (s), 2850 (s), 1730 (s), 1468 (s), 1374 (s), 1176 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H), 1.30-1.38 (m, 4H), 1.34 (d, J = 6.4 Hz, 3H), 1.40-1.67 (m, 6H), 3.15 (dq, J = 3.2, 6.4 Hz, 1H), 4.13 (q, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 22.4, 23.4, 25.7, 27.2, 27.5, 31.8, 35.3, 60.5, 67.4, 173.8; mass spectrum *m/z* (relative intensity) EI 214 (0. 1, M^+), 197(13), 169 (100), 157 (26), 141 (14), 99 (82), 81 (77), 55 (83); HRMS (ESI) calculated for $[C_{12}H_{22}O_3Na]^+$: 237.1461, found 237.1458.

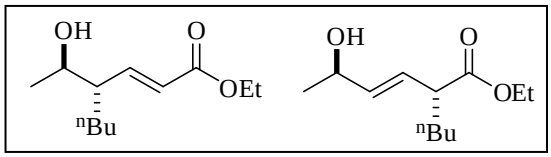
6-*anti*-(*n*-Butyl)-4-methyl-3-oxabicyclo-[3.1.0]-hexen-2-one (59a).[103] Employing general



procedure B and using ^{n}BuLi (1.2 mL, 2.5 M in hexane, 3.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl γ,δ-epoxy-α,β-hexenoate (156 mg, 1.0 mmol) in CH_2Cl_2 after purification by flash column chromatography (silica, 10-20 % EtOAc:petroleum ether, v/v) gave pure **59a** (138 mg, 82 %) as a colorless oil which was reported in the literature.[103] IR (neat) 2921 (s), 2856 (s), 1765 (s), 1456 (s), 1194 (s), 1007 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.20-1.33 (m, 2H), 1.36 (d, J = 6.4 Hz, 3H), 1.38-1.45 (m, 4H), 1.87 (dd, J = 5.5, 1.9 Hz, 1H), 1.98 (dq, J = 5.9, 3.6 Hz, 1H), 4.79 (dq, J = 6.4, 4.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9,

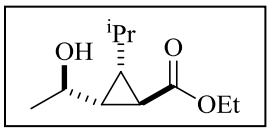
17.7, 22.2, 22.7, 25.4, 28.8, 30.7, 31.0, 75.9, 175.9; mass spectrum *m/z* (relative intensity) EI 168 (0.11, M^+), 153 (55), 124 (17), 100 (47), 99 (56), 81 (100), 68 (99), 55 (64), 53 (66).

(*E*) (4S*,5R*) Ethyl 4-butyl-5-hydroxy-2-hexenoate (56a) and (*E*) (2R*, 5R*) Ethyl-2-butyl-5-hydroxy-3-hexenoate (56a). The 1-hexyne (164 mg, 2.0 mmol) was deportonated on treating



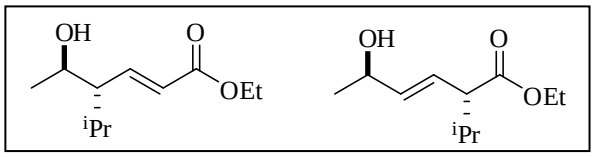
with ^{n}BuLi (0.8 mL, 2.5 M in hexane, 2.0 mmol) in THF under argon by using the literature procedure.[127] Employing general procedure**B**, at -20 ^{o}C, 1-hexynyllithium (2.0 mmol), ^{n}BuLi (0.4 mL, 2.5 M in hexane, 1.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl *γ,δ* -epoxy-*α,β*-hexenoate (156 mg, 1.0 mmol) after purification by flash column chromatography (silica, 10-20 % EtOAc:petroleum ether, v/v) gave the mixture of **56a** and **57a** (120 mg, 56 %, regioisomeric ratio = 76:24) as a colorless oil. **56a**: IR (neat) 3440 (br s), 2958 (s), 2929 (s), 2860 (s), 1732 (s), 1458 (m), 1368 (m), 1250 (m), 1176 (s), 968 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.18 -1.25 (m, 8 H), 1.27(t, *J* = 7.3 Hz, 3H), 1.30-1.34 (m, 1H), 4.17 (q, *J* = 3.2 Hz, 2H), 5.84 (d, *J* = 16.1 Hz, 1H), 6.8 (d, *J* = 9.6 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.4, 21.2, 22.8, 29.6, 30.3, 50.5, 60.5, 69.9, 123.9, 149.4, 166.4; mass spectrum *m/z* (relative intensity) EI 214 (8, M^+), 197 (8), 171 (14), 158 (37), 153 (43), 144 (27), 140 (27), 129 (28), 125 (52), 112 (69), 101 (99), 83 (75), 67 (48), 55 (100). **57a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.4 Hz, 6H), 1.12-1.33 (m, 8H), 1.43-53 (m, 1H), 1.63 (s, 1H), 1.69-1.75 (m, 1H), 2.92 (q, *J* = 7.3 Hz, 1H), 4.10 (q, *J* = 7.3 Hz, 2H), 5.56-5.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.3, 22.5, 23.4, 29.3, 32.3, 48.9, 60.6, 68.6, 128.3, 136.7, 174.6; mass spectrum *m/z* (relative intensity) EI 214 (0.03, M^+), 170 (90), 142 (14), 127 (97), 124 (37), 99 (100), 81 (62), 70 (14), 55 (46).

(1R*, 2R*, 3S*, 1'R*) Ethyl 2-(1-hydroxyethy)-3-(1-methylethyl)-cyclopropane carboxylate (58b). Employing general procedure B and using ^{i}PrMgCl (0.50 mL, 2.0 M in Et_2O, 1.0 mmol),



MeLi (1.25 mL, 1.6 M in diethyl ether, 2.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl *γ,δ*-epoxy-*α,β*-hexenoate (156 mg, 1.0 mmol) after purification by flash column chromatography (silica, 10-20% EtOAc:petroleum ether, v/v) gave **58b** (138 mg, 69 %, dr 100:0) as a colorless oil (the application of General procedure D gave 160 mg, 80%, 100:0 dr): IR (neat) 3448 (br s), 2941 (br s), 2868 (s), 1727 (s), 1471 (s), 1370 (s), 1179 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 1.19 (t, J = 4.6 Hz, 1H), 1.27 (t, J = 6.8 Hz, 3H), 1.31-1.34 (m, 1H), 1.35 (d, J = 9.6 Hz, 3H), 1.36-1.42 (m, 1H), 1.10 (s, 1H), 1.65 (dt, J = 5.0, 9.6 Hz, 1H), 3.53 (dq, J = 3.2, 6.4 Hz, 1H), 4.12 (q, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.8, 23.0, 23.9, 24.4, 27.4, 35.2, 36.1, 60.5, 67.1, 173.8; mass spectrum *m/z* (relative intensity) EI 200 (0.3, M^+), 155 (55), 32 (128), 110 (98), 99 (100), 69 (35), 56 (54); Anal.Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07 %. Found: C, 65.87; H, 10.2 %.

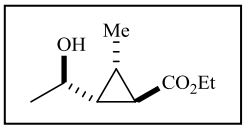
(*E*) (4S*,5R*) Ethyl 2-(1-methylethyl)-5-hydroxy-3-hexenoate (56b) and (*E*) (2R*,5R*) Ethyl 4-(1-methylethyl)-5-hydroxy-2-hexenoate (57b). Employing general procedure B and



using ^{i}PrMgCl (0.50 mL, 2.0 M in diethyl ether, 1.0 mmol), MeLi (1.25 mL 1.6 M Et_2O, 2.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl *γ,δ*-epoxy-*α,β*-hexenoate (156 mg, 1.0 mmol) after flash column chromatography (silica, 10-20 % EtOAc:petroleum ether, v/v) gave the 1:1 mixture of **56b** and **57b** (36 mg, 18 %, regioisomeric ratio) as a colorless oil: IR (neat) 3444 (br s), 2965 (s), 2932 (s), 2874 (s), 1720 (s), 1370 (s), 1178 (s), 1154 (s), 1037 (s); **56b, 57b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H), 1.20 (d, J =

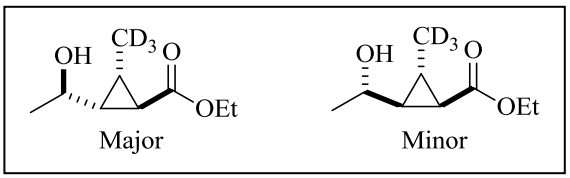
6.4 Hz, 3H), 1.27 (t, *J* = 5.0 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.31 (t, *J* = 6.9 Hz, 3H), 1.26-1.40 (m, 3H), 1.59 (s, 1H), 1.67 (s, 1H), 1.83-2.01 (m, 3H), 2.68 (t, *J* = 8.2 Hz, 1H), 4.01 (s, 1H), 4.15 (q, *J* = 6.8 Hz, 2H), 4.22 (q, *J* = 6.8 Hz, 2H), 4.32 (dt, *J* = 11.5, 5.5 Hz, 1H), 5.62-5.67 (m, 2H), 5.87 (d, *J* = 15.6 Hz, 1H), 6.90 (dd, *J* = 15.6, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (2 carbon), 19.4, 19.8, 20.7, 21.5, 22.0, 23.5, 28.4, 30.9, 56.6, 56.9, 40.4, 60.5, 67.5, 68.6, 124.9, 127.0, 137.8, 147.6, 166.2, 174.1; mass spectrum *m/z* (relative intensity) EI **56b**: 200 (0.02, M^+), 183 (0.8), 156 (99), 141 (98), 128 (20), 125 (18), 113 (97), 110 (65), 101 (70), 95 (100), 82 (60), 67 (60), 56 (97); **57b:** 200 (0.02, M^+), 182 (0.35), 175 (2), 157 (46), 143 (14), 125 (37), 109 (61), 97 (100), 83 (36), 69 (87), 55 (35).

(1R*,2R*,3S*,1'R*) Ethyl 2-(1-hydroxyethyl)-3-methylcyclopropane carboxylate (58c).



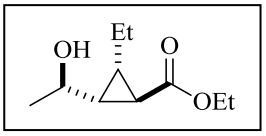
Employing general procedure**A** and using MeLi (1.88 mL, 1.6 M in Et_2O, 3.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl *γ,δ*-epoxy-*α,β*-hexenoate (156 mg, 1.0 mmol) at room temperature, after purification by flash column chromatography (silica, 20-30% EtOAc:petroleum ether, v/v) gave **58c** (113 mg, 65%, dr 100:0) as a colorless oil: IR (neat) 3432 (br s), 2967 (s), 2921 (s), 1715 (s), 1434 (s), 1361 (s), 1181 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.4 Hz, 3H), 1.24-1.14 (m, 1H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.35 (d, *J* = 7.8 Hz, 3H), 1.57 (dt, *J* = 2.8, 5.0 Hz, 2H), 1.81 (s, 1H), 3.49-3.1 (m, 1H), 4.11 (q, *J* = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 14.2, 21.3, 23.3, 26.2, 34.4, 60.5, 66.9, 173.6; mass spectrum *m/z* (relative intensity) EI 172 (0. 2, M^+), 154 (12), 127 (81), 98 (69), 83 (100), 69 (57), 59 (93), 55 (76); Anal.Calcd for $C_9H_{16}O_3$; C, 62.77; H, 9.36 %. Found: C, 62.56; H, 9.24 %.

(1R*,2R*,3S*,1'R*) Ethyl 2-(1-hydroxyethyl)-3-methyl-d_3-cyclopropane carboxylate (58c')



Methyllithium-d_3 was prepared from CD_3I by using literature procedure.[128] Employing general procedure **A** and using methyl lithium-d_3 (3.0 mL, 1.0 M in diethyl ether, 3.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl γ,δ-epoxy-α,β-hexenoate (156 mg, 1.0 mmol) after purification by flash column chromatography (silica, 20-30% EtOAc:petroleum ether, v/v) gave **58c'** (117 mg, 67%, dr 97:3) as a colorless oil: **Major** IR (neat) 3423 (br s), 2977 (s), 2931 (s), 1723 (s) 1448 (s), 1271 (s), 1181 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 5.0 Hz, 1H), 1.26 (t, J = 7.3 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H), 1.57-1.62 (m, 2H), 1.70 (s, 1H), 3.43 (dq, J = 7.3, 13.3 Hz,1H), 4.05 (q, J = 6.8 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 10.86-11.78 (sept), 14.2, 21.1, 23.3, 26.1, 34.4, 60.5, 67.0, 173.6; mass spectrum *m/z* (relative intensity) EI 175 (0.11, M^+), 157 (9), 130 (83), 118 (100), 102 (37), 100 (32), 90 (99), 72 (88), 58 (82). **Minor** ^{1}H NMR all hydrogen were imbedded underneath major isomer; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.2, 23.6, 25.9, 29.7, 34.4, 60.3, 67.4, 174.1.

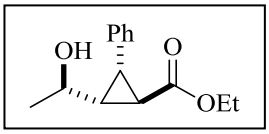
(1R*,2R*,3S*,1'R*) Ethyl 2-(1-hydroxyethyl)-3-ethylcyclopropane carboxylate (58g).



Employing general procedure C and using EtMgCl (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ethyl γ,δ-epoxy-α,β-hexanoate (156 mg, 1.0 mmol) after purification by flash column chromatography (silica, 15-25% EtOAc:petroleum ether, v/v) gave **58g** (136 mg, 73%, dr 100:0) as a colorless oil: IR (neat) 3437 (br s), 2957 (s), 2921 (s), 1717 (s), 1427 (s), 1364 (s), 1130 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 4.6 Hz, 1H), 1.26 (t, J = 6.9 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.38-1.45 (m, 1H), 1.48-1.53 (m, 1H), 1.61 (s, 1H), 1.62-1.69 (m, 2H), 3.15 (dq, J = 5.9, 12.3 Hz, 1H), 4.13 (q, J = 7.3 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 20.7, 23.5, 25.0, 29.3, 34.8, 60.5, 67.2, 173.7; mass spectrum *m/z* (relative intensity) EI 186 (0.04, M^+), 170 (0.1),

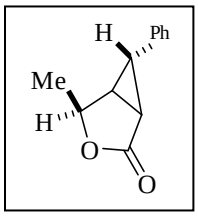
141 (68), 129 (52), 113 (28), 101 (62), 83 (36), 67 (26), 43 (100). HRMS (ESI) calculated for $[C_{10}H_{18}O_3Na]^+$: 209.1148, found 209.1140.

(1R*,2R*,3S*,1'R*) Ethyl 2-(1-hydroxyethyl)-3-phenylcyclopropane carboxylate (58e).



Employing general procedure B and using PhMgBr (0.36 mL, 2.8 M in Et_2O, 1.0 mmol), MeLi (1.25 mL, 1.6 M in Et_2O, 2.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl *γ,δ*-epoxy-*α,β*-hexenoate (156 mg, 1.0 mmol) in Et_2O, after purification by flash column chromatography (silica, 15-20% EtOAc:petroleum ether, v/v) gave **58e** (74 mg, 32 %, dr 100:0) as a colorless oil. Utilization of General Procedure E gave **58e** (157 mg, 61 %) as a mojor product: IR (neat) 3425 (br s), 2976 (s), 2890 (s), 1724 (s), 1447 (s), 1180 (s), 699 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, J = 6.4 Hz, 3H), 1.24 (t, J = 7.3 Hz, 3H), 1.41 (s, 1H), 1.82-1.87 (m, 1H), 1.99 (t, J = 4.3 Hz, 1H), 2.80 (dd, J = 4.1, 9.2 Hz, 1H), 3.14 (dq, J = 6.4, 9.6 Hz, 1H), 4.12 (q, J = 6.9 Hz, 2H), 7.17-7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.5, 23.3, 30.7, 35.9, 60.9, 66.4, 127.0, 128.5, 128.7, 135.4, 172.9; mass spectrum *m/z* (relative intensity) EI 234 (0.16, M^+), 216 (0.1), 189 (100), 177 (28), 161 (21), 144 (49), 143 (32), 133 (42), 128 (85), 117 (84), 115 (95), 107 (28), 91 (44), 77 (23), 55 (8); HRMS (ESI) calculated for $[C_{14}H_{18}NaO_3]^+$: 257.1154, found: 257.1148.

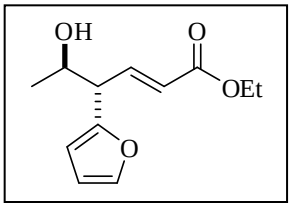
6-*anti*-(Phenyl)-4-methyl-3-oxabicyclo-[3.1.0]-hexen-2-one (59e). Employing general



procedure D, at -20 ^oC, PhMgBr (0.43 mL, 2.8 M in Et_2O, 1.0 mmol), flame dried $Zn(CN)_2$ (12 mg, 0.1 mmol) and ethyl *γ,δ*-epoxy-*α,β*-hexenoate (156 mg, 1.0 mmol) in Et_2O, after purification by flash column chromatography (silica, 15-20% EtOAc:petroleum ether, v/v) gave **59e** (13 mg, 7%) as a minor product. ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (d, J = 5.9 Hz, 3H), 2.26 (dd, J = 2.3, 5.5 Hz, 1H), 2.30 (t, J = 2.7 Hz, 1H), 2.40-2.43 (m, 1H), 4.80 (dq, J = 1.4, 5.9 Hz, 1H), 6.99-7.24 (m, 5H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 25.7, 28.7, 30.9, 76.6, 125.9, 127.1, 128.7, 137.2, 174.7; mass

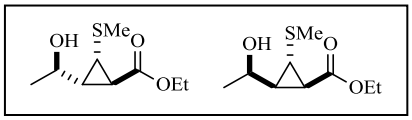
spectrum *m/z* (relative intensity) EI 188 (40, M^+), 144 (100), 143 (65), 129 (95), 117 (36), 115 (97), 91 (26), 89 (20), 77 (16), 65 (15), 55 (17). HRMS (ESI) calculated for $[C_{12}H_{12}O_2Na]+$: 211.0730, found 211.0731.

(*E*) (4S*,5R*) Ethyl 4-(2-furanyl)-5-hydroxy-2-hexenoate (56d). In a first flask, furan (0.08



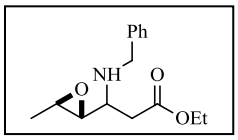
mL, 1.0 mmol) was deprotonated at 0 ^oC using ^nBuLi (0.4 mL, 2.5 M in hexane, 1.0 mmol) in THF (2.0 mL) under argon for 3 hours. In the second flask, to a solution of flame dried $ZnBr_2$ (225 mg, 1.0 mmol) in THF (2.0 mL) under argon was added MeLi (1.25 mL, 1.6 M in Et_2O, 2.0 mmol), 2-lithiofuran from flask 1 and the resulting mixture was stirred for 30 minutes at 0 ^oC. The flask was then *trans*ferred to a -20 ^oC bath, nitromethane (2.0 mL) was added and the stirred for additional 5 minutes. Next, ethyl 4,5-epoxy-2,3-hexenoate (156 mg, 1.0 mmol) was added and the resulting mixture was gradually warmed to room temperature over 12 hours. The reaction was quenched with NH_4Cl-NH_4OH aqueous buffer (pH = 7.0, 10.0 mL), filtered and the filtrate was extracted with Et_2O (3 x15.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10-20% EtOAc in petroleum ether, v/v) to give pure compounds **56d** (128 mg, 57%, dr 100:0) as a colorless liquid. [129] IR (neat) 3423 (br, s), 2921 (s), 2852 (s), 1718 (s), 1458 (s), 1262 (s), 1143 (s), 799 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, J = 5.9 Hz, 3H), 1.23 (t, J = 7.3 Hz, 3H), 1.92 (s, 1H), 3.48 (dd, J = 8.7, 5.9 Hz, 1H), 4.06-4.14 (m, 3H), 5.85 (d, J = 15.6 Hz, 1H), 6.25-6.27 (m, 1H), 7.06 (dd, J = 8.7, 15.6 Hz, 1H), 6.08 (d, J = 2.7 Hz, 1H), 7.30 (d, J = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 20.9, 49.9, 60.6, 69.2, 107.3, 110.5, 124.6, 142.1, 144.5, 152.9, 166.2; mass spectrum *m/z* (relative intensity) EI 224 (0.12, M^+), 206 (57), 178 (100), 139 (39), 133 (73), 128 (56), 111(71), 84 (63), 67 (44), 56 (17).

(1S*,2S*,3R*,1'R*) 1-Ethylcarboxy-2-thiomethyl-3-(1-hydroxylmethyl)-cyclopropane (58f) and (1S*,2S*,3S*,1'R*) 1-Ethylcarboxy-2-thiomethyl-3-(1-hydroxylmethyl)-cyclopropane

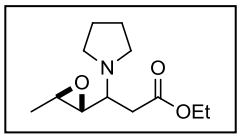


(58f'). Thiomethanol was deporonated in THF using NaH (1.0 equiv) at 0 ^{o}C for 15 minutes. Employing general procedure A and using epoxyenoate (156 mg, 1.0 mmol), thiomethanol (144 mg, 3.0 mmol), NaH (69 mg, 3.0 mmol) and $ZnBr_2$ (225 mg, 1.0 mmol) after purification by column chromatography gave the mixture of **58f** and **58f'** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 6.9 Hz, 6H), 1.30 (d, J = 5.5 Hz, 3H), 1.34 (d, J = 5.1 Hz, 3H), 2.15 (s, 3H), 2.19 (s, 3H), 2.49-2.59 (m, 3H), 2.76-2.79 (m, 3H), 2.85-3.03 (m, 6H), 4.15-4.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.2, 17.2, 17.3, 36.2, 37.1, 43.2, 44.1, 53.0, 55.3, 60.7, 60.8, 61.3, 61.6, 170.7, 170.8.

Ethyl 3-(1-aminomethylphenyl)-4,5-epoxy hexanoate (61a). Epoxyenoate **55** (156 mg, 1.0 mmol) was mixed with benzyl amine (1.0 mmol) in a Elynmyer flask in the absence of solvents and ran in the normal microwave for assigned power and indicated time. The reaction mixture was subjected to the column chromatography with out any aqueous work up (silica, 2% MeOH in CH_2Cl_2, v/v) affording pure **61a** as a colorless oil (218 mg, 83%, dr 67:33); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, J = 1.9 Hz, 3H), 1.17 (t, J = 6.9 Hz, 3H), 1.23 (d, J = 5.0 Hz, 6H), 2.20 (br s, 2H), 2.41-2.84 (m, 14H), 3.80 (dq, J = 31.2, 13.3 Hz, 4H), 4.03-4.08 (m, 4H), 7.14-7.28 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (2-carbon), 17.1, 17.2, 37.2 (2-carbon), 51.4, 51.8, 52.1, 55.0, 56.0, 56.2, 60.5, 60.6, 60.8, 62.0, 127.0, 127.8, 128.1 (2-carbon), 128.3, 128.4, 139.7, 140.0, 171.3, 171.9; mass spectrum *m/z* (relative intensity) EI 263 (0.3, M^+), 206 (35), 176 (12), 132 (6), 107 (5), 106 (51), 91 (100), 77 (3), 65 (9).



Ethyl 3-(1-pyrrolidinyl)-4,5-epoxy hexanoate (61b). Stirring the mixture of epoxyenoate **55**

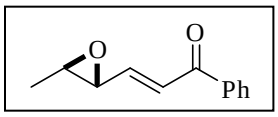


(1.0 equiv) with pyrrolidine (1.2 equiv) in MeOH at room temperature for 48h gave **61b** as a colorless oil (175 mg, 77%, 70:30 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J = 5.1 Hz, 3H), 1.21 (t, J = 5.5 Hz, 3H), 1.25 (d, J = 5.6 Hz, 3H), 1.31 (d, J = 5.1 Hz, 3H), 1.72 (br s, 8H), 2.30-2.81 (m, 18H), 4.07 (q, J = 6.4 Hz, 2H), 4.12 (q, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 14.0, 17.0, 17.2, 23.3 (2-carbon), 36.2, 36.8, 51.4, 51.9 (2-carbon), 56.8 (2-carbon), 60.3, 60.5 (2-carbon), 60.8, 62.7, 171.3, 171.8.

General Procedure F: Synthesis of Ketodiene. Ketodienes used for the reactions were synthesized by using the procedure as shown. To a solution of LDA (12.0 mL 1.0 M in THF) was added ketone (10.0 mmol in 10.0 mL THF) over 10 minutes at -78 ^{o}C. After 75 minutes, the mixture of crotonaldehyde (0.70 g, 10.0 mmol) with TMSCl (1.08 g, 10.0 mmol) in THF (5.0 mL) was added drop wise. The solution was removed from the cooling bath, stirred at room temperature for one hour before refluxing for 4 hours. The reaction was quenched with saturated NH_4Cl solution, diluted with water, extracted with dichloromethane (3 x 15 mL). The combined organic phase was washed with water (15.0 mL), brine (15.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo. The NMR of the product was identical with the one reported in the literature.[105]

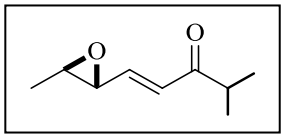
***(2E*,4R*,5R*)-4,5-Epoxy-1-phenylhex-2-en-1-one (63).**[121, 122] Employing general proecudre F and using LDA (18.0 mL 1.0 M in THF), acetophenone (1.8 g, 15.0 mmol), crotonaldehyde (1.05 g, 15.0 mmol) and TMSCl (1.62 g, 15.0 mmol) gave (*2E, 4E*)-1-phenyl-2,4-hexadien-1-one (1.73 g, 12.5 mmol) as a colorless oil. To the solution of 2*E*,4*E*-1-phenyl-2,4-hexadien-1-one (10.0 mmol) was added *m*-CPBA (3.0 g, 1.3 equiv, 75% wt. in water) at 0 ^{o}C in CH_2Cl_2 and the resulting mixture was warmed to the room temperature over 12 hours. The reaction mixture was

quenched with Me_2S (1.0 mL), diluted with water (10.0 mL) and extracted with CH_2Cl_2 (3 x 20.0 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 x 20.0 mL), brine (20.0 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The purification of product using flash column chromatography (silica, 10-15 % EtOAc: petroleum ether, v/v) gave pure **63** (1.52



g, 81%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, J = 5.0 Hz, 3H), 3.01-3.04 (m, 1H), 3.31 (dd, J = 6.8, 1.9 Hz, 1H), 6.82 (dd, J = 6.9, 15.5 Hz, 1H), 7.20 (d, J = 14.6 Hz, 1H), 7.47-7.96 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 57.7, 57.9, 126.9, 128.6, 128.7, 133.1, 137.3, 144.6, 189.6; mass spectrum *m/z* (relative intensity) EI 188 (M^+, 2), 172 (31), 120 (15), 105 (100), 77 (93), 55 (29).

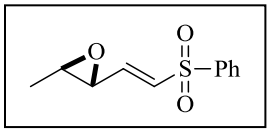
(*2E*,4R*,5R*)-4,5-Epoxy-1-(1-methylethyl)-hex-2-en-1-one (64). Employing general procedure F and using LDA (18.0 mL 1.0 M in THF), methyl isopropyl ketone (1.29 g, 15.0 mmol), crotonaldehyde (1.05 g, 15.0 mmol) and TMSCl (1.62 g, 15.0 mmol) gave (*2E, 4E*)-1-methylethyl-2,4-hexadien-1-one (1.73 g, 12.5 mmol) as a colorless oil. To the solution of (*2E, 4E*)-1-(1-methylethyl)-2,4-hexadien-1-one (1.38 g, 10.0 mmol) in CH_2Cl_2 was added *m*-CPBA (1.3 equiv, 3.0 g, 75 % wt. in water) at 0 ^{o}C and the resulting mixture was warmed to room temperature over 4 hours. The reaction mixture was quenched with Me_2S (1.0 mL), diluted with water and extracted with CH_2Cl_2 (3 x 20.0 mL). The organic layer was washed with saturated



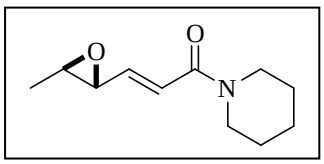
aqueous $NaHCO_3$ (5 x 20.0 mL), brine (20.0 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo after purification by flash column chromatography (silica, 10-15% EtOAc: petroleum ether, v/v) gave **64** (1.2 g, 78 %) as a colorless oil: IR (neat) 2972 (s), 2933 (s), 2875 (s), 1698 (s), 1674 (s), 1631 (s), 1466 (s), 1383 (s), 1237 (s), 980 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J = 6.8 Hz, 6H), 1.28 (d, J = 5.0 Hz, 3H), 2.68 (sept, J = 6.8 Hz, 1H), 2. 87 (dq, J = 4.2, 5.0 Hz, 1H), 3.08 (d, J = 6.8 Hz, 3H), 6.35-6.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 18.3, 39.1, 57.6 (2-carbons), 129.6,

142.4, 202.9; mass spectrum *m/z* (relative intensity) EI 154 (0. 18, M^+), 138 (0.97), 110 (26), 95 (100), 83 (67), 67 (18), 55 (36). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%; found: C, 69.73; H, 9.01%.

(*2E*,4R*,5R*)-3,4-Epoxy-1-phenylsulfonyl-2-pentene (65). 1-Phenylsulfonyl-(*1E,3E)*-pentadiene was prepared by using the procedure reported in the literature.[130] To the ice cold solution of (*1E,3E)*-1-phenylsulfonylpentadine (1.29 g, 6.2 mmol) in CH_2Cl_2 (30.0 mL) was added *m*-CPBA (1.3 equiv, 1.84 g, 75% wt. in water) and the mixture was warmed to the room temperature over 12 hours. The reaction was quenched with Me_2S (1.0 mL), diluted with water (10.0 mL) and extracted with CH_2Cl_2 (3 x 15.0 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 x 15.0 mL), water (15.0 mL), brine (15.0 mL), dried with anhydrous $MgSO_4$, filtered, concentration in vacuo gave after purification by flash column chromatography (silica, 15-25% EtOAc in petroleum ether, v/v) **65** (1.07 g, 77%) as a colorless solid: m.p. 83.7-86.1 ^oC; IR (neat) 3058 (s), 2999 (s), 2930 (s), 1631 (s), 1448 (s), 1308 (s), 1150 (s), 1087 (s), 965 (s), 798 (s), 747 (s), 689 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (dd, J = 2.5, 4.5 Hz, 3H), 2.93 (dq, J = 1.8, 5.0 Hz, 1H), 3.21 (d, J = 5.9 Hz, 1H), 6.62 (d, J = 15.2 Hz, 1H), 6.78-6.82 (dd, J = 6.0, 15.1 Hz, 1H), 7.53-7.88 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 56.0, 58.3, 127.8, 129.5, 132.4, 137.7, 139.9, 142.7. Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39 %; found: C, 58.97; H, 5.39%.

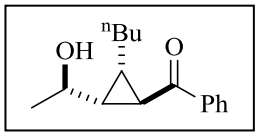


(*2E*,4R*,5R*)-4,5-Epoxy-1-piperidinohex-2-en-1-amide (66).[108, 131] Using the literature procedure,[108] sorbic acid (1.12 g, 10.0 mmol), triethyl amine (2.7 mL, 20.0 mmol), methane sulfonyl chloride (1.07 g, 15.0 mmol) and piperidine (0.88 mL, 15.0 mmol) gave colorless crystal of 2,4-hexadienoyl piperidine (57 %). To the solution of (*2E, 4E*)-2,4-hexadienoyl piperidine (1.79 g,



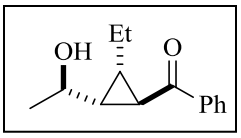
10.0 mmol) in CH_2Cl_2 was added *m*-CPBA (1.3 equiv, 3.0 g, 75% wt. in water) at 0 ^oC and the resulting mixture was warmed to room temperature over 12 hours. The reaction mixture was quenched with Me_2S (1.0 mL), diluted with water (10.0 mL) and extracted with CH_2Cl_2 (3 x 20.0 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 x 15.0 mL), brine (15.0 mL), dried over anhydrous $MgSO_4$, filtered and concentration in vacuo followed by purification with flash column chromatography (silica, 30-40% EtOAc in petroleum ether, v/v) gave **66** (1.33 g, 68%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (dd, J = 1.4, 5.0 Hz, 3H), 1.15-1.62 (m, 6H), 2.87-2.91 (m, 1H), 3.13 (dd, J = 1.8, 3.6 Hz, 1H), 3.43 (s, 2H), 3.54 (s, 2H), 6.53 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 24.6, 25.6, 26.7, 43.2, 47.0, 57.7, 57.9, 128.9, 141.1, 164.4.

(1R*,2R*,3S*,1'R*) 2-(1-Hydroxyethyl)-3-butyl cyclopropyl-1-phenyl ketone (67a).

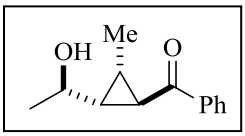


Employing general procedure C and using ^nBuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 4,5-epoxy-1-phenylhex-2-en-1-one **63** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 15-25 % EtOAc:petroleum ether, v/v) **67a** (184 mg, 74%, dr 100:0) as a white amorphous solid: m.p. 65.9-67.4 ^oC; IR (neat) 3429 (br s), 2959 (s), 2931 (s), 2860 (s), 1661 (s), 1415 (s), 1354 (s), 1225 (s), 702 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H), 1.36 (d, J = 5.9 Hz, 3H), 1.38-1.41 (m, 2H), 1.46-1.15 (m, 4H), 1.77-1.82 (m, 2H), 1.95 (dt, J = 4.6, 9.6 Hz, 1H), 2.32 (t, J = 4.1 Hz, 1H), 3.71 (dt, J = 3.6, 6.8 Hz, 1H), 7.49-8.0 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.5, 23.6, 27.5, 30.1, 31.7, 31.9, 38.0, 67.3, 127.9, 128.6, 132.8, 137.7, 198.8; mass spectrum *m/z* (relative intensity) EI 246 (0.3, M^+), 228 (0.4), 201 (99), 185 (8), 159 (14), 145 (23), 133 (15), 117 (8), 105 (100), 91 (11), 77 (58), 55 (15); HRMS (ESI) calculated for $[C_{16}H_{22}NaO_2]^+$: 269.1512, found 269.1503.

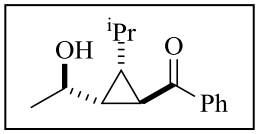
(1R*,2R*,3S*,1'R*) 2-(1-Hydroxyethyl)-3-ethylcyclopropyl-1-phenyl ketone (67b). Employing general procedure C and using EtMgCl (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 4,5-epoxy-1-phenylhex-2-en-1-one **63** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 15-25% EtOAc:petroleum ether, v/v) **67b** (137 mg, 63%, dr 100:0) as a white amorphous solid: m.p. 71.3-74.1 °C; IR (neat) 3431 (br s), 296 (s), 2918 (s), 1663 (s), 1446 (s), 1347 (s), 1234 (s), 706 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, J = 7.3 Hz, 3H), 1. 37 (d, J = 5.9 Hz, 3H), 1.53-1.57 (m, 1H), 1.61 (s, 1H), 1.76-1.84 (m, 2H), 1.94-1.99 (m, 1H), 2.30 (t, J = 4.6 Hz, 1H), 3.69 (dq, J = 5.9, 9.6 Hz, 1H), 7.48-7.99 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 21.3, 23.7, 30.1, 33.6, 38.3, 67.4, 128.0, 128.7, 132.9, 137.9, 198.9; mass spectrum *m/z* (relative intensity) EI 218 (0.02, M^+), 200 (0.18), 185 (4), 173 (62), 145 (17), 105 (100), 77 (48), 55 (7); HRMS (ESI) calculated for $[C_{14}H_{18}O_2Na]^+$: 241.1199 found 241.1196.



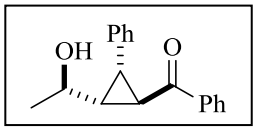
(1R*,2R*,3S*,1'R*) 2-(1-Hydroxyethyl)-3-methylcyclopropyl-1-phenyl ketone (67c). Employing general procedure C and using MeMgCl (0.4 mL, 3.0 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 4,5-epoxy-1-phenylhex-2-en-1-one **63** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 20-30% EtOAc:petroleum ether, v/v) **67c** (115 mg, 57%, dr 100:0) as a white amorphous solid: m.p. 72.3-74.3 °C; IR (neat) 3421 (br s), 2970 (s), 2929 (s), 1660 (s), 1450 (s), 1341 (s), 1223 (s), 701 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36-1.38 (m, 6H), 1.53 (s, 1H), 1.83-1.95 (m, 2H), 2.31 (t, J = 4.6 Hz, 1H), 3.73 (dt, J = 6.4, 13.6 Hz, 1H), 7.48-7.99 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 23.4, 25.1, 31.2, 37.9, 67.2, 127.9, 128.5, 132.8, 137.8, 198.8; mass spectrum *m/z* (relative intensity) EI 204 (0.1, M^+), 171 (13), 159 (98), 145 (22), 131 (14), 115 (90), 105 (100), 91 (11), 77 (94), 55 (22); HRMS (ESI) calculated for $[C_{13}H_{16}O_2Na]^+$: 227.1043, found 227.1030.



(1R*,2R*,3S*,1'R*) 2-(1-Hydroxyethyl)-3-(1-methylethyl)-cyclopropyl-1-phenyl ketone (67d). Employing general procedure C and using ^{i}PrMgCl (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 4,5-epoxy-1-phenylhex-2-en-1-one **63** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 20-30% EtOAc:petroleum ether, v/v) **67d** (146 mg, 63%, dr 100:0) as a white amorphous solid: m.p. 67.3-69.8 ^{o}C; IR (neat) 3421 (br s), 2964 (s), 2928 (s), 2871 (s), 1660 (s), 1450 (s), 1364 (s), 1223 (s), 703 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, J = 6.4 Hz, 3H), 1.17 (d, J = 6.4, 3H), 1.25-1.28 (m, 1H), 1.34 (d, J = 5.9 Hz, 3H), 1.42-1.46 (m, 1H), 1.59-1.66 (m, 1H), 1.97 (td, J = 3.6, 8.7 Hz, 1H), 2.30 (t, J = 4.5 Hz, 1H), 3.70 (dq, J = 5.5, 9.6 Hz, 1H), 7.47-7.89 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 23.3, 24.0, 27.9, 29.3, 38.8, 40.4, 67.2, 127.9, 128.6, 132.8, 137.8, 198.8; mass spectrum *m/z* (relative intensity) EI 232 (0.45, M^+), 214 (4), 199 (11), 187 (16), 171 (67), 149 (91), 145 (52), 131 (65), 117 (100), 105 (56), 91 (90), 77 (61), 1 (21); HRMS (ESI) calculated for $[C_{15}H_{20}O_2Na]^+$: 255.1356, found 255.1350.

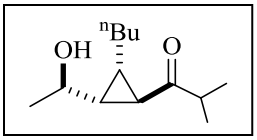


(1R*,2R*,3S*,1'R*) 2-(1-Hydroxyethyl)-3-phenylcyclopropyl-1-phenyl ketone (67e). Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in hexane, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) and 4,5-epoxy-1-phenylhex-2-en-1-one **63** (188 mg, 1.0 mmol) in toluene gave after flash column chromatography (silica, 15-25% EtOAc:petroleum ether, v/v) **67e** (170 mg, 64 %, dr 92:8) as a white solid: m.p. 69.7-71.3 ^{o}C; IR (neat) 3401 (br s), 2962 (s), 2921 (s), 1656 (s), 1449 (s), 1097 (s), 741 (s), 699 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, J = 6.4 Hz, 3H), 1.45 (s, 1H), 2.11-2.14 (m, 1H), 2.03-2.06 (m, 2H), 3.37 (dq J = 6.6, 9.6 Hz, 1H), 7.19-8.00 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 27.7, 33.9, 38.9, 66.6, 127.1, 128, 128.5, 128.7, 128.8, 133.1, 135.9, 136.8, 198.0; mass spectrum *m/z* (relative intensity) EI 248 (0.52, M^+-H_2O), 233 (5), 222



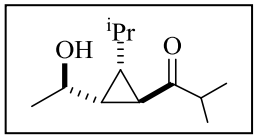
(27), 221 (100), 209 (6), 207 (12), 193 (4), 144 (8), 129 (9), 115 (15), 105 (65), 91 (6),77 (31), 65 (52); HRMS (ESI) calculated for $[C_{18}H_{18}NaO_2]^+$: 289.1199, found 289.1195.

(1R*, 2R*, 3S*, 1'R*) 2-(1-Hydroxyethyl)-3-butylcyclopropyl-1-(methylethyl) ketone (68a). Employing general procedure C and using ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$



(23 mg, 0.1 mmol) and 4,5-epoxy-1-(1-methylethyl)-hex-2-en-1-one **64** (154 mg, 1.0 mmol) in THF gave after flash column chromatography (silica, 15-25 % EtOAc:petroleum ether, v/v) **68a** (188 mg, 88%, dr 100:0) as a white solid: m.p. 52.7-54.5 ^{o}C; IR (neat) 3433 (br s), 2966 (s), 2931 (s), 2873 (s), 1687 (s), 1467 (s), 1382 (s), 1143 (s), 1074 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.13 (d, J = 6.8 Hz, 6H), 1.31 (d, J = 6.4 Hz, 3H), 1.33-1.45 (m, 4H), 1.15-1.56 (m, 1H), 1.60 (t, J = 4.5 Hz, 1 H), 1.64-1.72 (m, 3H), 1.75 (s, 1H), 2.71 (sept., J = 6.8 Hz, 1H), 3.56 (dt, J = 5.9, 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 18.1 (2 carbons), 22.4, 23.4, 27.2, 30.6, 31.7, 31.9, 37.2, 41.6, 67.1, 212.9; mass spectrum *m/z* (relative intensity) EI 212 (0.1, M^+), 195 (2), 169 (88), 167 (100), 115 (22), 123 (77), 109 (66), 95 (40), 81 (99), 69 (66), 55 (99). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39%; found C, 73.50; H, 11.56%.

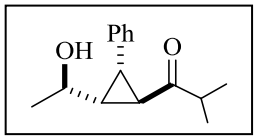
(1R*,2R*,3S*,1'R*) 2-(1-Hydroxyethyl)-3-(1-methylethyl)-cyclopropyl-1-methylethyl ketone (68d). Employing general procedure C and using ^{i}PrMgCl (0.6



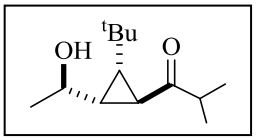
mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 4,5-epoxy-1-(1-methylethyl)-hex-2-en-1-one **64** (154 mg, 1.0 mmol) in THF gave after flash column chromatography (silica, 20-25% EtOAc:petroleum ether, v/v) gave **68d** (164 mg, 82%, dr 95:5) as a white solid: m.p. 61.8-63.4 ^{o}C; IR (neat) 3362 (br s), 2965 (s), 2870 (s), 1686 (s), 1467 (s), 1365 (s), 1143 (s), 1068 (s) cm^{-1}; **Major**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 3.2 Hz, 3H), 1.15 (d, J = 3.2 Hz, 3H), 1.25-1.28 (m, 1H),

1.31 (d, J = 5.9 Hz, 3H), 1.34-1.47 (m, 2H), 1.59 (t, J = 4.5 Hz, 1H), 1.71 (dt, J =8.7 Hz, 1H), 2.71 (septet, J = 6.8 Hz, 1H), 3.1 (dq, J = 6.4, 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2 (2-carbons), 22.7, 23.1, 23.9, 27.6, 30.8, 38.0, 39.3, 41.6, 67.1, 212.9; mass spectrum *m/z* (relative intensity) EI 198 (0.06, M^+), 180 (1.5), 155 (96), 153 (99), 137 (36), 125 (20), 109 (99), 99 (99), 95 (98), 83 (53), 71 (100), 69 (94), 55 (92); Anal. Calcd for $C_{12}H_{22}O_{2:}$ C, 72.68; H, 11.18 %; found: C, 72.83; H, 11.02%.

(1R*,2R*,3S*,1'R*) 2-(1-Hydroxyethyl)-3-phenyl cyclopropyl-1-methylethyl ketone (68e). Employing general procedure D and using PhMgBr (0.43mL, 2.8 M in Et_2O, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) and 4,5-epoxy-1-(1-methylethyl)-hex-2-en-1-one **64** (154 mg, 1.0 mmol) in CH_2Cl_2 gave after flash column chromatography (silica, 15-25% EtOAc:petroleum ether, v/v) **68e** (195 mg, 84%, dr 100:0) as a white solid: m.p. 61.3-62.4 ^{o}C IR (neat) 3422 (br s), 2971 (s), 2856 (s), 1687 (s), 1459 (s), 1386 (s), 1059 (s), 698 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.4 Hz, 3H), 1.41 (s, 1H), 1.84-1.88 (m, 1H), 2.36 (t, J = 5.0 Hz, 1 H), 2.74-2.81 (m, 2H), 3.22 (dq, J = 6.6, 9.6 Hz, 1H), 7.18-7.27 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 18.1, 22.6, 29.1, 33.1, 38.4, 41.9, 66.4, 127, 128.4, 128.7, 135.9, 211.8; mass spectrum *m/z* (relative intensity) EI 232 (0.23, M^+), 218 (0.5), 205 (4), 19 (17), 190 (40), 176 (5), 165 (52), 164 (93), 149 (100), 121 (20), 104 (12), 91 (12), 77 (13), 65 (3); HRMS (ESI) calculated for $[C_{15}H_{20}NaO_2]^+$: 255.1356, found 255.1322.

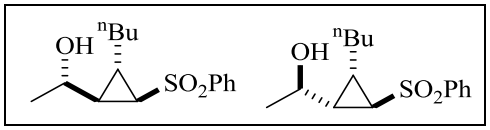


(1R*,2R*,3S*,1'R*) Ethyl 2-(1-hydroxyethyl)-3-(2,2-dimethylethyl)-1-methylethyl ketone (68f). Employing general procedure A, ^{t}BuLi (2.0 mL 1.5 M THF and toluene, 3.0 mmol), flame dried $ZnBr_2$ (225 mg, 1.0 mmol) and 4,5-epoxy-1-(1-methylethyl)-hex-2-en-1-one **7** (154 mg, 1.0 mmol) gave after purification by flash



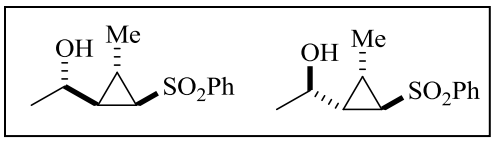
column chromatography (silica, 20-30% EtOAc:petroleum ether, v/v) **68f** (155 mg, 73%, dr 100:0) as a white solid. Utilization of general procedure C and using ^{t}BuMgCl (0.71 mL, 1.70 M in THF, 1.2 mmol, $ZnBr_2$ (23 mg, 0.1 mmol) and **64** (154 mg, 1.0 mmol) gave **68f** (174 mg, 82%, 100:0 dr): m. p. 67.8-69.3 ^{o}C; IR (neat) 3441 (br s), 2966 (s), 2851 (s), 1693 (s), 1470 (s), 1053 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (br s, 9H), 1.15 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.44-1.48 (m, 1H), 1.67 (dt, J = 9.7, 4.6 Hz, 1H), 1.69 (s, 1H), 1.86 (t, J = 5.1 Hz, 1H), 2.72 (sept, J = 7.4 Hz, 1H), 3.75 (qd, J = 10.1, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 18.3, 24.7, 27.9, 30.2, 31.2, 39.0, 41.6, 42.8, 66.8, 213.5; mass spectrum m/z (relative intensity) EI 212 (0.001, M^+), 194 (M^+-H_2O, 0.18), 167 (23), 143 (8), 125 (17), 109 (24), 99 (26), 83 (17), 71 (46), 57 (23), 55 (26), 43 (100). Anal. Calcd for $C_{13}H_{24}O_{2:}$ C, 73.54; H, 11.39 %; found: C, 73.92; H, 11.20 %.

(1R*,2R*,3S*,1'R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-*n*-butyl cyclopropane (69a) and **(1R*,2S*,3S*,1′R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-*n*-butyl cyclopropane (69a').** Employing general procedure C and using ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **65** (224 mg, 1.0 mmol) in THF after purification with flash column chromatography (silica, 25-35% EtOAc:petroleum ether, v/v) gave the mixture of **69a** and **69a'** (220 mg, 78%, dr 58:42) as a white solid. The reaction in CH_2Cl_2 gave 234 mg, 83%, dr 0:100 and in toluene gave 215 mg, 89%, dr 0:100: **69a:** m.p. 80.1-81.6 ^{o}C; IR (neat) 3449 (br s), 2960 (s), 2927 (s), 2859 (s), 1306 (s), 1147 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J = 7.0 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H), 1.25-1.36 (m, 5H), 1.59 (s, 1H), 1.67-1.70 (m, 1H), 1.84-1.89 (m, 2H), 2.05 (t, J = 5.0 Hz, 1H), 3.53 (dq, J = 6.0, 8.5 Hz, 1H), 7.57-7.91 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 22.2, 23.2, 25.3, 26.1, 31.5, 31.9, 43.8, 66.2, 127.6, 129.2, 133.3, 140.6; mass spectrum *m/z* (relative intensity) EI 282 (3, M^+) 281



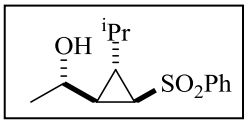
(9), 265 (1), 225 (78), 206 (29), 190 (4), 147 (17), 123 (87), 96 (6), 77 (66), 73 (100), 55 (89). Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.80; H, 7.85 %; found: C, 64.07; H, 8.02 %. **69a':** m.p. 83.2-84.7 ^oC; IR (neat) 3448 (br s), 2960 (s), 2929(s), 2859 (s), 1306 (s), 1147 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, J = 7.3 Hz, 3H), 1.09-1.28 (m, 5H), 1.37 (d, J = 5.9 Hz, 3H), 1.38-1.44 (m, 1H), 1.65 (s, 1H), 1.90-1.95 (dt, J = 6.8, 13.0 Hz, 1H), 2.24 (dd, J = 5.5, 8.7 Hz, 1H), 2.38 (d, J = 1.8 Hz, 1H), 4.36 (dq, J = 6.4, 13.3 Hz, 1H), 7.57-7.93 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 22.1, 23.8, 25.2, 30.9, 32.0, 37.5, 45.0 64.5, 127.3, 129.2, 133.4, 141.4; mass spectrum *m/z* (relative intensity) EI 282 (0.3, M^+), 265 (1), 237 (27), 225 (80), 195 (13), 143 (39), 123 (96), 97 (40), 77 (66), 57 (63), 55 (100).

(1R*,2S*,3S*,1'R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-methyl cyclopropane (69c').

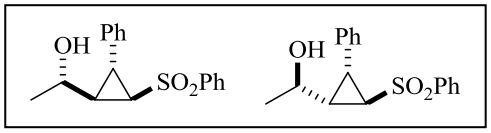


Employing general procedure C and using MeMgCl (0.53 mL, 2.3 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **65** (224 mg, 1.0 mmol) in toluene gave after purification with flash chromatography (silica, 25-35% EtOAc:petroleum ether, v/v) **69c'** with minor **69c** (201 mg, 83%, dr 93:7) as colorless solid. **Major:** IR (neat) 3499 (br s), 2972 (s), 2933 (s), 2872 (s), 1447 (s), 1305 (s), 1146 (s), 1091 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 5.9 Hz, 3H), 1.34 (d, J = 6.4 Hz, 3H), 1.39 (q, J = 6.9 Hz, 1H), 1.97- 2.06 (m, 1H), 2.24 (dd, J = 5.4, 8.7 Hz, 1H), 2.37 (s, 1H), 4.35 (dq, J = 6.4, 13.3 Hz, 1H), 7.56-7.93 (m, 5H); ^{13}C NMR(125MHz, $CDCl_3$) δ 17.2, 19.7, 23.9, 38.2, 45.5, 64.7, 127.1, 129.3, 133.4, 141.7; mass spectrum *m/z* (relative intensity) EI 240 (0. 14, M^+), 223 (2), 183 (100), 161 (7), 143 (24), 125 (49), 99 (87), 83 (55), 77 (67), 55 (37); HRMS (ESI) calculated for $[C_{12}H_{16}O_3SNa]^+$: 263.0712, found 263.0711. **Minor:** ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, J = 5.9 Hz, 3H), 1.25 (d, J = 6.4 Hz, 3H), 1.25-1.27 (m, 1H), 2.03-2.06 (m, 2H), 3.49-3.53 (m, 2H), 7.56-7.90 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 19.2, 23.0, 31.7, 44.3, 65.9, 127.5, 129.2, 133.5, 140.5; mass

spectrum *m/z* (relative intensity) EI 242 (0.14, M^+), 223 (2), 195 (4), 143 (10), 125 (21), 99 (100), 77 (38), 55 (22).

(1R*,2S*,3S*,1′R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-(1-methylethyl)-cyclopropane (69d'). 

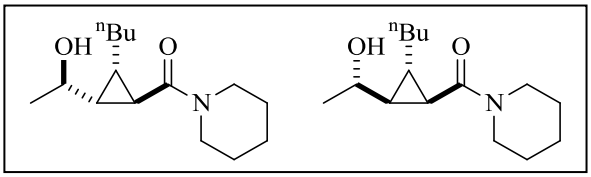
Employing general procedure C and using ^{i}PrMgCl (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **65** (224 mg, 1.0 mmol) intoluene gave after purification with flash column chromatography (silica, 30-35% EtOAc:petroleum ether, v/v) **69d'** (235 mg, 87%, dr 100:0) as a colorless solid: m. p. 87.4-88.6 ^{o}C; IR (neat) 3504 (br s), 2962 (s), 1448 (s), 1303 (s), 1148 (s), 1091(s), 734 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H), 1.25-1.29 (m, 1H), 1.38 (d, J = 6.4 Hz, 3H), 1.40-1.45 (dd, J = 7.3, 14.2 Hz, 1H), 1.73 (q, J = 6.9 Hz, 1H), 1.91 (s, 1H), 2.28 (dd, J = 5.5, 8.7 Hz, 1H), 4.37 (dt, J = 6.4, 12.4 Hz, 1H), 7.57-7.94 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.4, 23.7, 31.5, 32.6, 36.9, 44.5, 64.3, 127.5, 129.2, 133.5, 141.3; mass spectrum *m/z* (relative intensity) EI 268 (0.12, M^+), 215 (55), 223 (40), 211 (93), 195 (5), 143 (29), 125 (68), 109 (100), 83 (55), 77 (63), 59 (78), 55 (63); HRMS (ESI) calculated for $[C_{14}H_{20}O_3SNa]^+$: 291.1031, found 291.1037.

(1R*,2R*,3S*,1'R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-phenyl cyclopropane (69f) and **(1R*,2S*,3S*,1'S*) 1-(1-Hydroxyethyl)-2-(phenyl sulfonyl)-3-phenyl cyclopropane (69f').** 

Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in Et_2O, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **65** (224 mg, 1.0 mmol) in CH_2Cl_2 gave after purification with flash column chromatography (silica, 15-20%, EtOAc:petroleum ether, v/v) gave the mixture of **69f** and **69f'** (263 mg, 87%, dr 4:96) as a white amorphous solid. **Minor** (**69f,** 11 mg): m.p. 89.1-91.2 ^{o}C; IR (neat) 3410 (br s), 2926 (s), 2852

(s), 1410 (s), 1311 (s), 1150 (s), 750(s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (d, J = 6.4 Hz, 3H), 1.30 (s, 1H), 2.17 (ddd, J = 5.0, 9.2, 14.2 Hz, 1H), 2.81 (t, J = 4.9 Hz, 1H), 2.18-3.24 (m, 1H), 3.30 (dd, J = 5.1, 9.7 Hz, 1H), 7.24-7.35 (m, 5H), 7.63 (t, J = 7.3 Hz, 2H), 7.71 (t, J = 6.9 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 28.9, 37.9, 46.7, 64.6, 126.8, 127.2, 127.3, 128.6, 129.4, 133.7, 137.2, 141.1; mass spectrum *m/z* (relative intensity) EI 302 (0.1, M^+), 284 (0.3), 245 (1), 207 (4), 162 (13), 161 (100), 143 (32), 128 (24), 117 (23), 115 (42), 105 (5), 91 (33), 77 (27), 65 (7), 55 (11); HRMS (ESI) calculated for $[C_{17}H_{18}NaO_3S]^+$: 325.0869, found 325.0857. **Major** (**69f'**, 252 mg): m.p. 91.2-93.4 ^oC; IR (neat) 3370 (br s), 3063 (s), 3030 (s), 2926 (s), 1596 (s), 1495 (s), 1453 (s), 1233 (s), 1017 (s), 766 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, J = 6.4 Hz, 3H), 1.98 (q, J = 7.3, 1H), 2.37 (s, 1H), 2.74 (dd, J = 5.4, 9.1 Hz, 1H), 3.15 (t, J = 5.9 Hz, 1H), 4.54 (dq, J = 6.4, 12.8 Hz, 1H), 6.98-7.98 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 28.9, 37.9, 46.7, 64.6, 126.8, 127.2, 127.3, 128.6, 129.4, 133.7, 137.2, 141.1; mass spectrum *m/z* (relative intensity) EI 302 (0.1, M^+), 284 (0.2), 245 (1), 207 (7), 162 (12), 161 (100), 143 (33), 129 (23), 117 (24), 115 (42), 91 (33), 77 (27), 65 (7), 55 (12); HRMS (ESI) calculated for $[C_{17}H_{18}NaO_3S]^+$: 325.0869, found 325.0861.

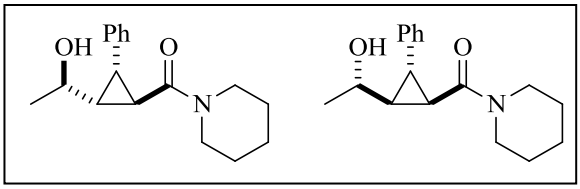
(1R*,2R*,3S*,1'R*)2-[-1-Hydroxylethyl]-3-butyl-1-*N,N*-cyclohexylenecyclopropanecarboxamide (70a) and **(1R*,2S*,3S*,1'R*) 2-[-1-hydroxylethyl]-3-butyl-1-*N,N*-cyclohexylenecyclopropanecarboxamide (70a').** Employing general procedure C and using ^{n}BuMgCl (0.48



mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 4,5-epoxy-1-piperidinohex-2-en-1-amide **66** (195 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) the mixture of **70a** and **70a'** (121 mg, 48%, dr 59:41) as a colorless oil. **Major (70a,** 71 mg): IR (neat) 3409 (br s), 2931 (s), 2857 (s), 1617 (s), 1456 (s), 1139 (s) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.35 (d, J = 5.9 Hz, 3H), 1.36-1.72 (m, 16H), 3.56 (s, 5H); ^{13}CNMR (125 MHz, $CDCl_3$) 14.0, 22.5, 23.6, 23.8, 24.7, 25.5, 26.4, 26.8, 27.4, 32.2, 33.6, 43.3, 46.7, 67.6, 170.5; ^{1}H NMR (500 MHz, benzene-d_6) δ 0.87-0.89 (m, 6H), 1.10-1.1 (m, 14H), 1.68-1.74 (m, 1H), 1.80-1.85 (m, 1H), 3.09 (s, 2H), 3.30-3.35 (m, 1H), 3.50 (s, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ 14.6, 23.1, 23.3, 24.2, 24.4, 25.3, 26.8, 28.0, 32.8, 34.4, 43.7, 46.8, 67.5, 170.4; mass spectrum *m/z* (relative intensity) EI 253 (0.4, M^+), 235 (37), 220 (4), 208 (100), 196 (13), 166 (5), 152 (8), 138 (8), 112 (29), 84 (60), 69 (42), 55 (32); HRMS (ESI) calculated for $[C_{15}H_{27}NO_2Na]^+$: 276.1934, found 276.1931. **Minor (70a'):** 50 mg; IR (neat) 3409 (br s), 2931 (s), 2857 (s), 1617 (s), 1456 (s), 1139 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.07-1.11 (m, 1H), 1.25 (d, J = 5.9 Hz, 3H), 1.29-1.74 (m, 14H), 3.54-3.64 (m, 4H), 3.71 (s, 1H), 3.91-3.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 23.0, 23.4, 24.6, 25.6, 26.6, 31.4, 33.1, 57.7, 43.3, 47.1, 64.2, 170.7; ^{1}H NMR (500 MHz, benzene-d_6) δ 0.88 (t, J = 5.9 Hz, 3H), 1.06-1.35 (m, 14H), 1.38 (d, J = 6.4 Hz, 3H), 2.03 (t, J = 5.9 Hz, 1H), 3.03 (s, 2H), 3.44 (s, 2H), 4.04 (s, 1H), 4.22 (m, 1H), ^{13}C NMR (125 MHz, benzene-d_6) δ 14.6, 23.1, 23.4, 24.5, 25.1, 26.1, 27.1, 32.1, 33.9, 36.7, 43.5, 47.1, 64.7, 171; mass spectrum *m/z* (relative intensity) EI 253 (0.4, M^+), 235 (37), 208 (89), 196 (99), 166 (27), 112 (88), 84 (100), 81 (50), 69 (86), 55 (68); HRMS (ESI) calculated for $[C_{15}H_{27}NO_2]^+$: 254.2115, found 254.2111.

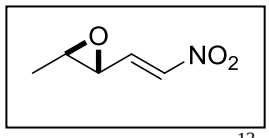
(1R*,2R*,3S*,1'R*) 2-[-1-Hydroxylethyl]-3-phenyl-1-*N*,*N*-cyclohexylene cyclopropane carboxamide (70e) and **(1R*, 2S*, 3S*, 1'R*) 2-[-1-hydroxylethyl]-3-phenyl-1-*N*,*N*-cyclo-



hexylenecyclopropanecarboxamide (70e'). Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in Et_2O, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) and 4,5-epoxy-1-pipperidinohex-2-en-1-amide **66** (195 mg, 1.0

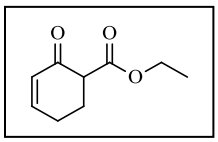
mmol) in toluene gave after purification with flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) the mixture of **70e** and **70e'** (180 mg, 66%, dr 19:81) as a colorless oil. IR (neat) 3421 (br s), 2911 (s), 2903 (s), 2841 (s), 1621 (s), 1451 (s), 1109 (s), 758 (s) cm^{-1}; **Major (70e'):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (d, J = 6.0 Hz, 3H), 1.57-1.76 (m, 8H), 2.05 (s, 1H), 2.89 (t, J = 6.0 Hz, 1H), 3.09 (br s, 1H), 3.57 (br s, 3H), 4.15 (dq, J = 10.6, 4.6 Hz, 1H), 7.15-7.35 (m, 5H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 24.6, 25.7, 26.6, 26.7, 28.5, 36.7, 43.5, 47.3, 64.4, 126.2, 128.5, 128.8, 140.9, 169.7; HRMS (ESI) calculated for $[C_{17}H_{23}NNaO_2]^+$: 296.1621, found 296.1607; **Minor (70e):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J = 10.6 Hz, 3H), 1.57-1.76 (m, 3H), 1.84-1.97 (m, 2H), 2.05-2.08 (m, 2H), 2.23 (t, J = 4.6 Hz, 1H), 2.85 (dd, J = 9.2, 5.5 Hz, 1H), 3.09 (br s, 1H), 3.29-3.34 (m, 1H), 3.64 (br s, 4H), 7.15-7.35 (m, 5H); ,^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 22.8, 24.7, 30.0, 35.4, 43.6, 47.2, 66.8, 126.9, 128.5, 128.6, 136.6, 169.6. HRMS (ESI) calculated for $[C_{17}H_{23}NO_2]^+$: 273.1723, found 273.1708.

Epoxidation of *2E, 4E*-Nitropentadiene. The *2E, 4E*-nitropentadiene used for the reactions was prepared using the literature procedure (see detailed synthetic procedure in chapter 5).[132] To the solution of nitrodiene (565 mg, 5.0 mmol) in CH_2Cl_2 was added *m*-CPBA (1.3 equiv, 1.5 g, 75%) and the resulting mixture was refluxed for 4 hours. Reaction mixture was cooled down to room temperature, quenched with Me_2S, diluted with water (10.0 mL) and extracted with CH_2Cl_2 (3 x 10.0 mL). The organic layer was washed with saturated $NaHCO_3$ (5 x 15.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$ and solvent was removed in rota vacuo. The purification product using flash column chromatography (silica, 2% EtOAc in petroleum ether) gave **71** (503 mg, 78%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (d, J = 5.1 Hz, 3H), 3.05 (dq, J = 5.1, 2.3 Hz, 1H), 3.27 (dd, J = 5.5, 1.4 Hz, 1H), 7.01-7.19 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 17.6, 54.0, 58.7, 139.1, 140.0.



Synthesis of Cyclic Epoxide

Preparation of ethyl 2-oxocyclohex-3-enecarboxylate: Ethyl 2-oxocyclohex-3-enecarboxylate

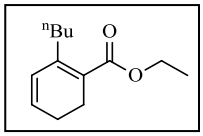


was synthesized by using the slight modification of literature procedure.[110] To a stirred solution of LiHMDS (15.75 mL, 1.0 M in THF, 15.75 mmol) in dry THF (30.0 mL) was added a solution of a cyclohexenone (1.44 g, 15.0 mmol) in dry THF (15.0 mL) slowly at -78 °C. After 30 min stirring at that temperature, a solution of ethyl cyanoformate (1.99 g, 15.0 mmol) in dry THF (10.0 mL) was added, the resulting mixture was stirred for one hour at -78 °C, and next allowed to warm to room temperature over 12 hrs. The reaction was quenched with saturated aqueous NH_4Cl solution, diluted with water (15.0 mL) and extracted with Et_2O (3 x 20.0 mL). The combined organic layer was washed subsequently with brine (10.0 mL) and water (10.0 mL) then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 1:4, EtOAc:petroleum ether) gave *β*-ketoesters **72** (2.1 g, 83%) as a colorless oil.[110] **Ethyl 2-oxocyclohex-3-enecarboxylate (72):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.3 Hz, 3H), 2.07-2.10 (m, 1H), 2.23-2.35 (m, 3H), 3.25 (m, 1H), 4.09 (q, J = 6.9 Hz, 2H), 5.92 (d, J = 10.1 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 14.2, 24.4, 25.7, 53.5, 61.3, 129.1, 150.8, 170.1, 190.1.

Preparation of ethyl-*2*-butyl-1,3-cyclohexadiene ester (74): The enol phosphate of *β*-keto ester was prepared by using the literature procedure.[112] To the ice cold solution of *β*-keto ester **72** (845 mg, 5.0 mmol) in dry Et_2O was added sodium hydride (132 mg, 5.5 mmol). After stirring for 30 min at 0 ^{o}C, diethyl chlorophosphate (1.3 g, 7.5 mmol) was added. The reaction flask was removed to room temperature and stirred for 4 hours before quenching with saturated aqueous NH_4Cl solution. The mixture was diluted with water (10.0 mL), extracted with Et_2O (3 x 15.0

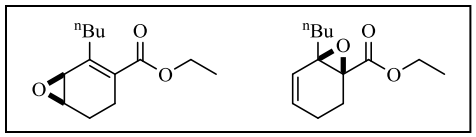
mL), washed subsequently with brine (15.0 mL) and water (15.0 mL), dried over anhydrous $MgSO_4$ and solvent was evaporated in rota vacuo.The product was purified by flash chromatography (silica, EtOAc:petroleum ether, 30:70; v/v) and used for cuprate reaction.

To the freshly prepared lithium di-*n*-butyl cuprate (3.0 mmol) in dry THF at -40 ^oC was added the



mixture of enol phosphate ester (608 mg, 2.0 mmol) and TMSCl (434 mg, 4.0 mmol) in THF (4.0 mL) slowly and the reaction mixture was warm up to room temperature over 12 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solutions, diluted with water (10.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic layer was washed subsequently with brine (10.0 mL) and water (10.0 mL) then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, EtOAc:petroleum ether, 5:95, v/v) gave ethyl *2-n*-butyl-1,3-cyclohexadiene ester **76** (304 mg, 73%) as colorless oil.[112] **Ethyl-*2*-Butyl-1,3-Cyclohexadiene Ester (74):** ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.30 (t, J = 7.4 Hz, 3H), 1.22-1.44 (m, 6H), 2.11-2.16 (m, 2H), 2.41 (t, J = 9.2 Hz, 1H), 2.51 (t, J = 7.8 Hz, 1H), 4.20 (q, J = 6.9 Hz, 2H), 5.92 (d, J = 9.7 Hz, 1H), 6.08 (td, J = 9.6, 4.6 Hz, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 14.1, 14.4, 22.9, 23.0, 23.6, 31.4, 33.4, 59.9, 121.4, 129.9, 132.3, 146.7, 168.6.

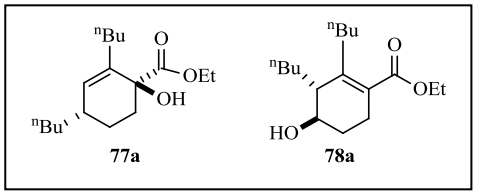
Epoxidation of Ethyl *2*-Butyl-1,3-Cyclohexadiene Ester: To the solution of ethyl *2-n*-butyl-



1,3-cyclohexadiene ester **74** (416 mg, 2.0 mmol) in CH_2Cl_2 (10.0 mL) was added *m*-CPBA (1.3 equiv, 0.59 g, 75% wt. in water), $NaHCO_3$ (378 mg, 4.5 mmol) and the resulting mixture was stirred at 0^oC for 4 hrs. Reaction mixture was quenched with Me_2S (0.5 mL), diluted with water (10.0 mL) and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (5 x 15.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered and

solvent was removed in rota vacuo. The purification of product by flash chromatography (silica, EtOAc:petroleum ether, 5:95, v/v) gave the mixture of *γ,δ*-epoxy-*β*-*n*-butyl substituted *α,β*-unsaturated cyclic ester **75** and *α,β*-epoxy-*β*-*n*-butyl substituted *γ,δ*- unsaturated esters **76** (296 mg, 71%, 80:20) as a colorless oil. **Major 75:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H), 1.20-1.57 (m, 5H), 2.01-2.41 (m, 4H), 2.67 (m, 1H), 3.19 (d, J = 4.6 Hz, 1H), 3.50 (s, 1H), 4.14 (q, J = 6.9 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 14.1, 14.3, 21.0, 21.6, 22.8, 31.1, 34.2, 52.0, 55.6, 60.5, 127.3, 144.8, 168.1. **Minor 76:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J = 6.85 Hz, 3H), 1.20-2.69 (m, 13H), 4.21 (q, J = 6.9 Hz, 2H), 5.77 (m, 1H), 5.94 (m, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 20.8, 23.3, 27.5, 31.7, 55.6, 60.6, 61.6, 66.6, 125.6, 133.9, 170.4.

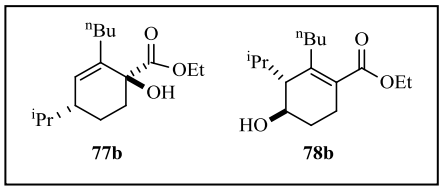
Ethyl-2,3-dibutyl-4-hydroxy-1-cyclohexene carboxylate (77a) and **Ethyl-1-hydroxy-2,4-dibutyl-2-cyclohexene carboxylate (78a).** Employing general procedure C and using $ZnBr_2$ (12 mg, 0.05 mmol) ^{n}BuMgCl (0.24 mL, 2.5 M in THF, 0.6 mmol) and epoxide **75** and **76** (mixture 4:1, 112 mg, 0.5 mmol) after purification by flash column chromatography (silica, 40-50% Et_2O: petroleum ether, v/v) gave **77a** and **78a** as colorless oil.



Ethyl-2,3-dibutyl-4-hydroxy-1-cyclohexene carboxylate (**77a**, 83 mg, 59%, dr 100:0): IR (neat) 3462 (br s), 2953 (s), 2946 (s), 2877 (s), 1718 (s), 1451 (s), 1261 (s), 1233 (s), 1079 (s) cm^{-1}; ^{1}H NMR (500 MHz, benzene-d_6) δ 0.85 (t, J = 6.5 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.03 (t, J = 6.9 Hz, 3H), 1.16-1.65 (m,13H), 1.96-2.08 (m, 2H), 2.32-2.57 (m, 1H), 2.50-2.57 (dt, J = 16.3, 8.3 Hz, 1H), 3.17-3.22 (m, 1H), 3.68 (s, 1H), 4.06 (t, J = 7.4 Hz, 2H); ^{13}C NMR (5125 MHz, benzene-d_6) δ 14.1, 14.2, 14.3, 22.6, 23.2, 23.4, 25.6, 30.1, 31.7, 32.2, 33.2, 47.3, 59.8, 67.4, 124.5, 149.7, 168.4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 6H), 1.30 (t, J = 6.9 Hz, 3H), 1.26-1.43 (m, 10H), 1.61 (m, 1H), 1.77-1.82 (m, 2H), 1.91 (dt, J = 13.8, 6.9 Hz, 1H), 2.14

(d, J = 9.2 Hz, 1H), 2.30-2.43 (m, 2H), 2.78-2.83 (m, 1H), 3.95 (m, 1H), 4.20 (q, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2-carbons), 14.2, 21.8, 22.8, 23.1, 24.7, 29.8, 31.4, 32.1, 32.8, 46.8, 60.1, 67.5, 123.9, 148.8, 168.9; mass spectrum *m/z* (relative intensity) 282 (0.2, M^+), 264 (5), 207 (45), 191 (40), 179 (20), 165 (12), 151 (21), 135 (40), 109 (23), 91 (26), 79 (30), 77 (13), 57 (100). **Ethyl-1-hydroxy-2,4-dibutyl-2-cyclohexene carboxylate** (**78a**, 6 mg, 4%, dr 100:0): IR (neat): 3422 (br s), 2957 (s), 2933 (s), 2872 (s), 1712 (s), 1458 (s), 1259 (s), 1227 (s), 1089 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (m, 6H), 1.26 (t, J = 6.9 Hz, 3H), 1.29-1.47 (m, 4H), 1.57-1.66 (m, 10H), 1.94-2.03 (m, 3H), 4.13 (q, J = 6.9 Hz, 2H), 4.16-4.19 (m, 1H), 5.65 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (2 carbons), 14.3, 22.8, 23.4, 26.4, 28.8, 29.5, 30.2, 31.3, 35.3, 49.9, 60.7, 66.9, 127.8, 141.4, 176.0; mass spectrum *m/z* (relative intensity) 282 (3, M^+), 264 (15), 237 (26), 222 (11), 207 (100), 193 (14), 179 (30), 161 (16), 140 (12), 133 (17), 123 (14), 107 (20), 93 (26), 79 (31), 57 (41), 55 (35)

Ethyl-2-butyl-3-(1-methylethyl)-4-hydroxy-1-cyclohexene carboxylate (77b) and **Ethyl-1-hydroxy-2-butyl-4-(1-methylethyl)-2-cyclohexene carboxylate (78b).** Employing general procedure C and using $ZnBr_2$ (12 mg, 0.05 mmol), ^{i}PrMgCl (0.30 mL, 2.0 M in Et_2O, 0.6 mmol), epoxides **75** and **76** (4:1 mixture, 112 mg, 0.5 mmol) after purification by flash column chromatography (silica gel, 40-50% Et_2O: petroleum ether, v/v) gave **77b** and **78b** as a colorless oil. **Ethyl-2-butyl-3-(1-methylethyl)-4-hydroxy-1-cyclohexene carboxylate** (**77b**, 76 mg, 57%,



dr 100:0): IR 3425 (br s), 2959 (s), 2933 (s), 2873 (s), 1713 (s), 1464 (s), 1235 (s), 1090 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 6.9 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 1.21-1.45 (m, 9H), 1.69-1.97 (m, 3H), 2.25 (m,1H), 2.42 (m, 1H), 2.80 (m, 1H), 4.01 (s, 1H), 4.21 (q, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.3, 19.7, 21.7, 22.1, 23.1, 27.1, 29.9, 31.2, 33.7, 52.9, 60.1, 66.3, 125.6, 148.6, 169.0; mass

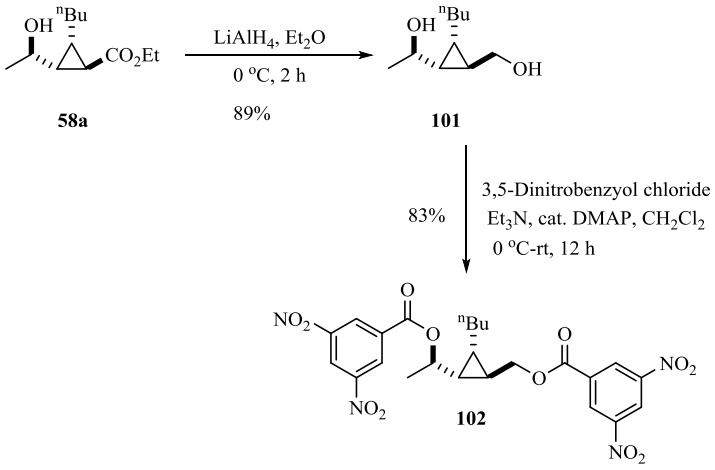
spectrum *m/z* (relative intensity) 268 (0.13, M^+), 250 (0.3), 207 (18), 195 (10), 179 (8), 161 (4), 152 (58), 137 (13), 123 (29), 109 (65), 95 (100), 91 (18), 81 (40), 67 (42), 55 (30). **Ethyl-1-hydroxy-2-butyl-4-(1-methylethyl)-2-cyclohexene carboxylate** (**78b**, 8 mg, 6%, dr 100:0): IR (neat) 3436 (br s), 2952 (s), 2943 (s), 2883 (s), 1719 (s), 1459 (s), 1241 (s), 1087 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 0.91 (d, J = 6.85 Hz, 3H), 0.94 (d, J = 6.85 Hz, 3H), 1.29 (t, J = 7.3 Hz, 3H), 1.26-1.41 (m, 5H), 1.64-2.07 (m, 8H), 4.18-4.29 (m, 2H), 5.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.2, 19.7, 21.8, 22.6, 30.3, 30.6, 31.9, 35.4, 41.1, 62.1, 74.6, 130.5, 136.8, 177.2; mass spectrum *m/z* (relative intensity) 268 (1.2, M^+), 250 (1), 195 (100), 177 (6), 161 (2), 151(6), 139 (16), 109 (11), 95 (9), 81 (11), 69 (14), 55 (8).

Reduction of 2-(1-hydroxyethyl)-3-butyl cyclopropane carboxylate (58a): To the solution of ethyl 2-(1-hydroxyethyl)-3-butyl cyclopropane carboxylate **58a** (214 mg, 1.0 mmol) in Et_2O (10.0 mL) was added $LiAlH_4$ (68 mg, 2.0 mmol) at 0 ^oC. The cloudy suspension was stirred for 2 hours before quenching subsequently with water (2.0 mL), 2N NaOH (2.0 mL) and water (2.0 mL) at 0 ^oC. Anhydrous $MgSO_4$ was added and the resulting mixture was filtered through a plug of celite eluting with Et_2O (25.0 mL) followed by solvent concentration in rota gave title compound **102** (152 mg, 89 %) which was used for the next step without purification.

General Procedure G for the synthesis of 3,5-dinitrobenzoyl derivative. The 3,5-dinitrobenzoyl derivatives was synthesized using modified literature procedure.[64] To the solution of cyclopropyl alcohol (1.0 equiv) in CH_2Cl_2 under argon was added Et_3N (1.5 equiv. per –OH group), 3,5-dinitrobenzoyl chloride (1.5 equiv per –OH group) and catalytic amount of DMAP (10-20 mg) and the resulting mixture was stirred for 12 hours at room temperature. Reaction mixture was quenched with saturated $NaHCO_3$ (5.0 mL), diluted with water (10.0 mL) and extracted with EtOAc (3 x 10.0 mL). The combined organic layer was washed with brine (10.0

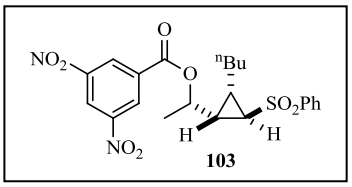
mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by column chromatography (silica, 1:9, EtOAc:petroleum ether, v/v) gave 3,5-dinitrobenzoyl derivatives.

(1R*,2R*,3R*,1'R*)-1-(1-(3,5-Dinitrobenzoyloxy)ethyl)-2-(1-(3,5-dinitrobenzoyloxy)-methyl)-3-*n*-butyl-cyclopropane (102). Employing general procedure G and using cyclopropane diol **101** (86 mg, 0.5 mmol), Et_3N (153 mg, 1.5 mmol), 3,5-dinitrobenzoyl chloride (523 mg, 1.5 mmol) and catalytic amount of DMAP (20 mg) in CH_2Cl_2 gave after purification by flash column chromatography (silica, 1:9; EtOAc:petroleum ether, v/v) **102** (232 mg, 83%) as colorless solid. The recrystallization of **102** in acetone using slow solvent evaporation process afforded a needle shaped crystal good for X-ray crystallography.



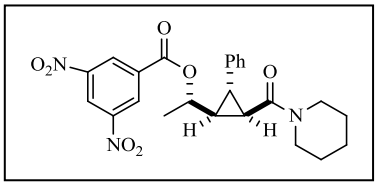
(1R*,2R*,3R*,1′R*)-1-(1-(3,5-Dinitrobenzoyloxy)ethyl)-2-(1-(3,5-dinitrobenzoyloxy)-methyl)-3-*n*-butylcyclopropane (102) : M. p. 96.6-98.5 ^oC; IR (neat) 2927 (m), 2891 (m), 1724 (s), 1633 (br), 1544 (s), 1459 (s), 1345 (s), 1273 (br), 1168 (s), 1075 (s), 721 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (t, J = 6.4 Hz, 3H), 1.10-1.53 (m, 8H), 1.58 (d, J = 5.9 Hz, 3H), 3.48 (q, J = 6.8 Hz, 1H), 4.36 (dd, J = 7.3, 11.4 Hz, 1H), 4.47 (dd, J = 6.9, 11.5 Hz, 1H), 4.99 (dt, J = 5.9, 12.3 Hz, 1H), 9.19-9.27 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.9, 22.3, 22.6, 23.8, 27.3, 27.8, 32.0, 70.1, 73.9, 122.3, 122.5, 129.3, 129.4, 133.9, 134.3, 148.7, 148.8, 161.7, 162.5.

(1R*,2R*,3S*,2'R*)-1-Phenylsulfonyl-2-(1-(3,5-dinitrobenzoyloxy)-ethyl)-3-*n*-butyl-cyclopropane (103). Employing general procedure G and using **69a** (28 mg, 0.1 mmol), Et_3N (15 mg, 0.15 mmol), 3,5-dinitrobenzoyl chloride (53 mg, 0.15 mmol) and DMAP (2 mg) in CH_2Cl_2 gave after purification by flash column chromatography (silica, 1:9, EtOAc:petroleum ether, v/v) **103** (38 mg, 80%) as yellowish solid. The compounds on recrystallization in acetone using slow solvent evaporation process afforded a needle shaped crystal good for X-ray crystallography. M. p. 102.3-105.4 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 0.72 (t, J = 6.5 Hz, 3H), 1.15-1.26 (m, 6H), 1.32 (d, J = 6.4 Hz, 3H), 1.91-1.97 (m, 1H), 2.18-2.24 (m, 2H), 4.94 (dq, J = 6.4, 9.6 Hz; 1H), 7.60-7.95 (m, 5H), 9.16 (s, 2H), 9.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.4, 22.1, 25.6, 26.3, 29.2, 29.8, 31.4, 44.2, 71.7, 122.7, 127.8, 129.5 (2-carbon), 133.8, 140.1, 148.8, 161.6.



103

(1R*,2S*,3S*,2'R*)-1-Piperidinylamido-2-(1-(3,5-dinitrobenzoyloxy)ethyl)-3-phenyl-cyclopropane (104). Employing general procedure G and using **70e'** (41mg, 0.15 mmol), Et_3N (23 mg, 0.23 mmol), 3,5-dinitrobenzoyl chloride (81 mg, 0.23 mmol) and DMAP (3 mg) in CH_2Cl_2 gave after purification by flash column chromatography (silica, 10% EtOAc in petroleum ether, v/v) **104** (61mg, 87%) as yellowish solid. The compounds on re-crystallization in CH_2Cl_2:EtOAc (1:1 mixture) using slow solvent evaporation process afforded a needle shaped crystal good for X-ray crystallography. M. p.101.2-104.7 ^oC; IR (neat) 2947 (s), 2911 (s), 2891 (s), 1740 (s), 1665 (b), 1513 (s), 1444 (s), 1367 (s), 1157 (s), 1105 (s), 739 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (d, J = 6.5 Hz, 3H), 1.61-1.74 (m, 6H), 1.92-1.99 (m, 1H), 2.28 (dd, J = 9.2, 3.7 Hz, 1H), 3.05 (t, J = 6.0 Hz, 1H), 3.60-3.66 (m, 4H), 5.50 (dt, J = 9.2, 6.4 Hz, 1H), 7.15-7.30 (m, 5H), 9.15-9.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 24.5, 26.2, 29.1, 33.3, 73.8, 122.1, 126.3, 126.6, 128.6, 129.5, 134.5, 139.7, 148.3, 161.6, 167.0; ^{13}C NMR

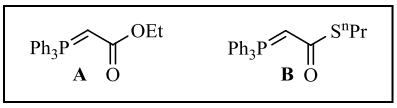


(125 MHz, benzene-d_6) δ 21.0, 25.0, 26.1, 27.1, 28.3, 30.0, 34.2, 43.7, 46.9, 74.2, 122.1, 126.9, 127.3, 129.1, 129.3, 134.1, 140.6, 148.5, 162.2, 167.3.

General Procedure H: Synthesis of Compounds 80-85. The *γ*-haloenoates used for the reactions was prepared by the modification of literature procedure.[133] To the solution of aldehyde (1.0 equiv) intoluene (3.0 mL/mmol) was added pyrrolidine (0.2 equiv) at -20 ^oC and the resulting solution was stirred for 5 minutes. Solid NXS or pthlimidoselenium chloride (1.3 equiv) was added on it at -20 ^oC and the mixture was stirred for further 2 hours at that temperature. The reaction flask was cooled to -40 ^oC bath and carbethoxymethylene triphenylphosphorane (1.35 equiv) solution in THF (2.0 mL/mmol) was added on it. The reaction flask was gradually warmed up to room temperature over 12 hrs, quenched with water, extracted with Et_2O (3 times), the combined organic layer was washed with saturated aqueous NH_4Cl solutions, dried over anhydrous $MgSO_4$, filtered, concentrated in rota vacuo and purified by flash column chromatography to give the title compounds.

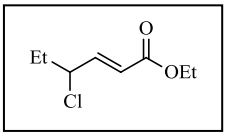
General Procedure I. Reaction of Grignard Reagents with 79-85 in the Presence of Catalytic Amounts of Zn(II) salts. To the solution of flame dried zinc (II) salts (0.1 equiv) in THF or CH_2Cl_2 or toluene was added *γ*-haloenoate or *γ*-selenoenoate at room temperature. Next, the reaction flask was cooled at indicated temperature, Grignard reagents (1.2 equiv) was added and stirred for indicated time at the given temperature. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O (3 times), the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo and purified by flash column chromatography to give the title compounds.

Synthesis of Ylides. The ylides **A** and **B** used for the reactions were prepared using the literature



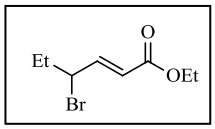
procedure as follows.[134] To the solution of triphenyl phosphine (13.1 g, 50 mmol) intoluene (50.0 mL) was added ethyl bromoacetate or propyl bromothioacetate (50.0 mmol) and the mixture was stirred for 2 hrs at 70 ^{o}C. The resulting solid was filtered and recrystallized in Et_2O. The recrystallized products was next dissolved in the mixture of EtOAc and dichloromethane (60.0 mL, 3:1 v/v) and treated with saturated NaOH solution until the solid get dissolved. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered and solvent removal in rota vacuo gave pale yellow solid. **A** (16.70 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, J = 7.3 Hz, 3H), 4.01 (q, J = 6.9 Hz, 2H), 7.40-7.63 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 30.7, 57.9, 128.7, 128.8, 132.0, 133.0, 133.1; **B** (17.58 g, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.59 (sext, J = 7.4 Hz, 2H), 2.81 (t, J = 7.3 Hz, 2H), 7.42-7.63 (m, 16H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 24.4, 30.6, 46.3, 47.1, 126.3, 127.0, 128.7, 128.8, 132.1, 132.8, 132.9.

(E) **Ethyl 4-chloro-2-hexenoate (81).**[124, 125] Employing general procedure G and using *n*-



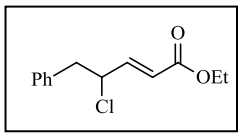
butanaldehyde (1.42 g, 20.0 mmol), pyrrolidine (142 mg, 2.0 mmol), NCS (3.47 g, 26.0 mmol) and carbethoxymethylene triphenylphosphorane (9.4 g, 27.0 mmol) after purification by column chromatography (5% EtOAc in petroleum ether, v/v) gave **81** (2.18 g, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.31 (t, J = 7.4 Hz, 3H), 1.81-1.96 (m, 2H), 4.21 (q, J = 6.90 Hz, 2H), 4.41 (q, J = 6.9 Hz, 1H), 6.03 (d, J = 15.6 Hz, 1H), 6.90 (dd, J = 15.1, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 14.1, 30.9, 60.7, 61.4, 122.6, 146.0, 165.9.

(E) **Ethyl 4-bromo-2-hexenoate (82).**[125] Employing general procedure G and using *n*-butanaldehyde (1.42 g, 20.0 mmol), pyrrolidine (142 mg, 2.0 mmol), NBS (4.63 g, 26.0 mmol)



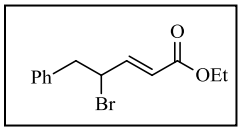
and carbethoxymethylene triphenylphosphorane (9.4 g, 27.0 mmol) after purification by column chromatography (5% EtOAc in petroleum ether, v/v) gave **82** (2.78 g, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3H), 1.28 (t, J = 6.9 Hz, 3H), 1.93-2.02 (m, 2H), 4.22 (q, J = 7.3 Hz, 2H), 4.48 (q, J = 6.9 Hz, 1H), 5.93 (d, J = 15.6 Hz, 1H), 6.95 (dd, J = 15.6, 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 14.0, 31.0, 52.9, 60.5, 121.8, 146.1, 165.5; mass spectrum *m/z* (relative intensity) EI 222 (M^+, 1.0), 220 (M^+, 1.0), 177 (10), 175 (10), 141 (100), 113 (56), 95 (38), 85 (27), 81 (24), 73 (30), 67 (51), 57 (20), 55 (51).

(E) **Ethyl 4-chloro-5-phenyl-2-pentenoate (83)**. Employing general procedure G and using 3-phenylpropanaldehyde (1.34 g, 10.0 mmol), pyrrolidine (71 mg, 1.0 mmol), *N*-chlorosuccinimide



(1.74 g, 13.0 mmol) and carbethoxy-methylene triphenylphosphorane (4.7 g, 13.5 mmol) after purification by column chromatography (5% EtOAc in petroleum ether, v/v) gave **83** (1.5 g, 63 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 6.9 Hz, 3H), 3.15 (d, J = 7.4 Hz, 2H), 4.20 (q, J = 6.90 Hz, 2H), 4.64 (q, J = 7.4 Hz, 1H), 5.96 (d, J = 15.1 Hz, 1H), 6.93 (dd, J = 15.6, 7.8 Hz, 1H), 7.19-7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 44.2, 60.1, 60.7, 123.1, 127.2, 128.5, 129.4, 136.2, 145.3, 165.7.

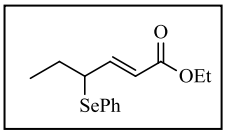
(E) **Ethyl 4-bromo-5-phenyl-2-pentenoate (84).** Employing general procedure G and using 3-



phenylpropanaldehyde (0.67 g, 5.0 mmol), pyrrolidine (71 mg, 1.0 mmol), NBS (1.16 g, 6.5 mmol) and carbethoxymethylene triphenylphosphorane 2.54 g, 6.75 mmol) after purification by column chromatography (5% EtOAc in petroleum ether, v/v) gave **88** (0.98 g, 69%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 6.9 Hz, 3H), 3.14-3.22 (m, 2H), 4.12 (q, J = 7.4 Hz, 2H), 4.64 (q, J = 7.4 Hz, 1H), 5.78 (d, J = 15.6 Hz,

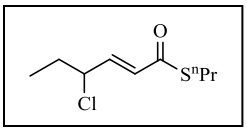
1H), 6.93 (dd, J = 15.6, 9.6 Hz, 1H), 7.09-7.25 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 44.4, 50.9, 60.7, 122.5, 127.2, 128.5, 129.2, 136.9, 145.7, 165.5.

(E) **Ethyl 4-selenophenyl-2-hexenoate (85).** Employing general procedure G and using *n*-



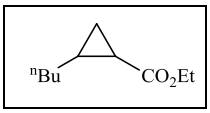
butanaldehyde (0.36 g, 5.0 mmol), pyrrolidine (71 mg, 1.0 mmol), *N*-phenylselenopthalimide (1.93 g, 6.5 mmol) and carbethoxymethylene triphenylphosphorane (2.54 g, 6.75 mmol) after purification by column chromatography (5% EtOAc in petroleum ether, v/v) gave **85** (1.0 g, 67 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H), 1.63-1.76 (m, 2H), 3.57 (q, J = 9.2 Hz, 1H), 4.08 (q, J = 6.9 Hz, 2H), 5.24 (d, J = 15.6 Hz, 1H), 6. 82 (dd, J = 15.6, 10.1 Hz, 1H), 7.19-7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 14.2, 26.8, 47.6, 60.2, 119.8, 128.0, 128.3, 128.9, 136.2, 147.6, 166.2.

(E) **Propyl 4-chloro-2-hexenylthionate.** Employing general procedure G and using *n*-



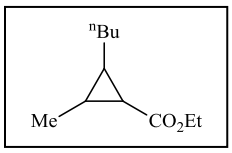
butanaldehyde (0.59 g, 8.2 mmol), pyrrolidine (117 mg, 1.64 mmol), *N*-chlorosuccimimide (1.42 g, 10.6 mmol) and thiocarbethoxymethylene triphenylphosphorane (3.96 g, 10.6 mmol) after purification by column chromatography (5% EtOAc in petroleum ether, v/v) gave propyl 4-chloro-2-hexenylthionate as a colorless oil (1.42 g, 69%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 3.7 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H), 1.60-1.69 (m, 2H), 1.85-1.96 (m, 2H), 2.96 (t, J = 7.4 Hz, 2H), 4.40 (q, J = 6.9 Hz, 2H), 6.30 (d, J = 15.1 Hz, 1H), 6. 81 (dd, J = 15.1, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 13.2, 22.8, 30.8, 30.9, 61.4, 129.0, 141.4, 189.6; mass spectrum *m/z* (relative intensity) EI 208 (M^+, 4.0), 206 (M^+, 10.5), 133 (34), 131 (100), 103 (10), 95 (67), 9 (8), 67 (34), 55 (9).

1-Ethylcarboxy-2-butylcyclopropane (86).[123] Using general procedure H and employing

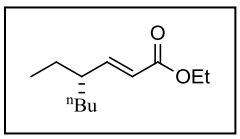


^{n}BuMgCl (1.2 mmol) and $ZnBr_2$ (23 mg, 0.1 mmol) and γ-bromoenoate **79** (1.0 mmol) after purification by column chromatography gave pure **86** (105 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 6.4 Hz, 3H), 1.26 (t, J = 7.4 Hz, 3H), 1.01 (t, J = 7.8 Hz, 2H), 1.22-1.61 (m, 9H), 4.12 (q, J = 6.90 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 15.5, 20.2, 22.3, 22.9, 31.2, 32.7, 60.2, 174.6.

1-Ethylcarboxy-2-butyl-3-methyl cyclopropane (87). Using general procedure H and employing ^{n}BuMgCl (0.71 mL, 1.7 M in THF, 1.2 mmol) and zinc bromide (23 mg, 0.1 mmol) and γ-bromo enoate **80** (1.0 mmol) after purification by column chromatography gave pure **87 (**116 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H), 1.28 (t, J = 7.8 Hz, 2H), 1.29-1.44 (m, 9H), 4.14 (q, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 14.0, 14.4, 22.3, 23.7, 25.7, 28.9, 31.2, 32.8, 60.0, 172.9; EI mass spectrum *m/z* (relative intensity) EI 184 (M^+, 0.6), 155 (37), 139 (40), 127 (100), 114 (7), 97 (31), 83 (44), 55 (57).



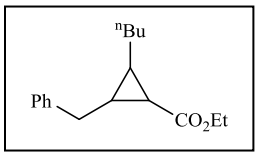
Ethylcarboxy-2-butyl-3-ethyl cyclopropane (88). Using general procedure H and employing



^{n}BuMgCl (0.71 mL, 1.7 M in THF, 1.2 mmol) and zinc bromide (23 mg, 0.1 mmol) and γ-bromo/chloro enoate **81** or **82** (1.0 mmol) after purification by column chromatography gave pure **88** (43-72%, dr at C3 6.5:1) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.8 Hz, 3H), 1.01 (t, J = 7.8 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H), 1.17-1.69 (m, 9H), 4.10 (q, J = 6.90 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 14.3, 20.1, 22.3, 25.2, 28.0, 31.2, 31.6, 32.8, 60.0, 172.9; EI mass spectrum *m/z* (relative intensity) EI 198 (M^+, 1.1), 169 (55), 153 (29), 141 (100), 123 (21), 113 (27), 101 (25), 95 (75), 83 (32), 81 (28), 69 (50), 55 (68). The minor amounts of ethyl-4-ethyl-2-

octenoate (**92**) was also observed in the reaction.[126] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 1.21 -1.49 (m, 11H), 2.05 -2.09 (m, 1H), 4.19 (q, J = 6.9 Hz, 2H), 5.80 (d, J = 15.6 Hz, 1H), 6.76 (dd, J = 15.6, 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 14.0, 14.3, 22.7, 27.2, 29.4, 33.8, 44.3, 60.1, 121.2, 153.7, 166.8.

1-Ethylcarboxy-2-butyl-3-(1-phenylmethyl)-cyclopropane (89). Employing general procedure G and using ^{n}BuMgCl (0.71 mL, 1.7 M in THF, 1.2 mmol) and zinc bromide (23 mg, 0.1 mmol) and γ-chloroenoate **83** (238 mg, 1.0 mmol) after purification by column chromatography gave pure **89** (198 mg, 76%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H), 1.28-1.41 (m, 7H), 1.50-1.57 (m, 2H), 2.87 (dd, J = 15.1, 7.5 Hz, 1H), 2.98 (dd, J = 14.5, 7.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 7.20-7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.3, 22.3, 25.5, 28.2, 30.4, 31.0, 32.7, 60.2, 125.8, 128.3 (2-carbons), 141.5, 172.9; mass spectrum *m/z* (relative intensity) EI 260 (M^+, 1.40), 215 (13), 203 (28), 188 (35), 186 (57), 157 (99), 129 (38), 117 (35), 104 (100), 91 (80), 77 (7), 65 (10).



X-Ray Crystallography Experimental: The proposed stereochemistry from NMR study was verified by a single crystal X-ray structure determination (for details see CIF files at Appendix A). A crystal of requesite sample was mounted in AFC8S diffractometer equipped with a Mercury CCD area detector and Mo Kα radiation (λ = 0.7071 Å). Diffraction data were collected in 0.5° oscillations of ω at reported temperature. Data were collected, processed and corrected for absorption and Lorentz and polarization effects using the Crystal Clear software package. The structure was solved by direct methods and refined by least squares refinement on F2 SHELXL software package absences of the data. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were constrained to idealized geometries and treated as riding atoms.

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CHAPTER III

REGIO- AND DIASTEREOSELECTIVE HALOFUNCTIONALIZATION REACTION OF FUNCTIONALIZED AND NON-FUNCTIONALIZED ALKENES

3.1 Introduction

Vicinal halofunctionalization of alkenes via halonium ion intermediate is a powerful method for introducing halogen to the target molecule in synthetic organic chemistry.[1] The vicinal halofunctionalization of alkenes for the syntheses of halofunctionalized natural products and drug targets is well reported in the literature.[2, 3] During the reaction, rehybridization of olefinic carbons from sp^2 to sp^3 occur with concomitant formation of upto two stereogenic centers in the molecule. The chemistry of chloro-, bromo- or iodo-functionalization of alkenes is significantly more explored and usually proceeds through halonium ion intermediates. The formation of halonium ion intermediates in the reaction of alkenes with halonium ion sources can be rationalized by the Lewis acid-Lewis base concept.[4] In these reactions, the π-system of alkenes act as a Lewis base which reacts to the electrophilic halogen of *N*-halosuccinimide (NXS, X = Cl, Br, I) that behave as Lewis acids. The donation of electron density from alkene to the electrophilic halogen and back donation of electrons on halogen to the alkene gives halonium ion intermediate. The S_N2 opening of halonium ion intermediate with nucleophile gives *anti*-addition product and hence the process is stereospecific.[5] To the contrary, a fluoro-functionalization reaction usually proceeds through carbenium ion intermediates and is a non-stereospecific process.[6]

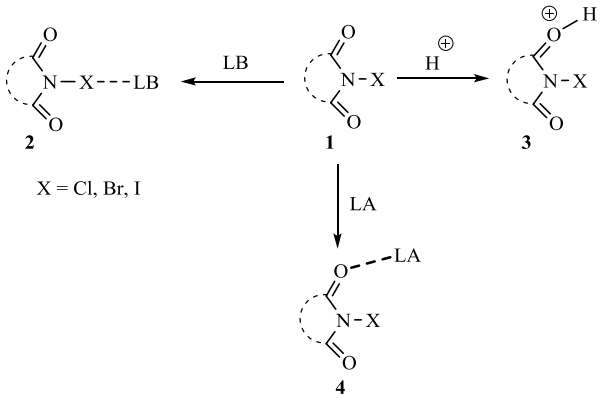
A variety of halogenating reagents including molecular halogen, *N*-halogen delivering reagents (e.g., *N*-halosuccinimide, *N*-halopthalimide, *N*,*N*-dihalo-*p*-toluenesulfonamide and 1,3-

dihalohydantoin) are commonly used for the halofunctionalization reaction. *N*-halo reagents transfer halonium ions or halogen free radicals to alkenes depending upon the reaction conditions under which reagents are used. *N*-Halosuccinimides are the reagent of choice in halofunctionalization reactions as these reagents are less reactive than molecular halogen and easier to handle. In addition, the by-product of the reaction (i.e., succinimide) is less nucleophilic and easily removed from the reaction.

A variety of catalysts are currently used for the halofunctionalization reaction of alkenes. These catalysts range from transition metal complexes to small organic molecules called organocatalyst. Transition metals have high capacity to bind with varieties of functional groups and formed the corresponding complexes. The reaction involving transition metal complexes exhibit variable oxidation state in the reaction and are valuable for designing asymmetric catalysts. The discovery of environmentally benign organocatalytic system allures the high interest of scientific community in recent years. Organocatalysts are less sensitive to air, moisture and usually they have lower cost and readily available in comparison to transition metal complexes. Organocatalysts that are used for halofunctionalization reactions include Lewis bases (LB),[4] Lewis acids (LA),[7] Brønsted acids[8] and phase transfer catalysts.[9] However, the way how these catalysts behave are different. These organocatalytst catalyze the reaction by activating the alkene and halonium ion source via hydrogen bonding, or proton transfer (**Scheme 3.1**). Lewis acids and Brønsted acids catalyze the reaction by enhancing the electrophilic character of the halonium ion source by selective coordination with the carbonyl moiety of NXS or by protonation of *N*-haloimides respectively. On the other hand, Lewis bases catalyze the reaction by partial coordination with halogen in NXS thereby forming polarized complexes.[4] In phase transfer catalysis, the halonium ion source and the reactant molecules are in the two different phases (e.g.,

the mixture of THF and ionic solvents) and the catalyst acts as a bridging ligand by bringing all the reactant molecules into the same phase to promote the halofunctionalization reaction.[4]

Scheme 3.1 Haloimide Activation by Brønsted Acids, Lewis Acids, Lewis Bases.[10]



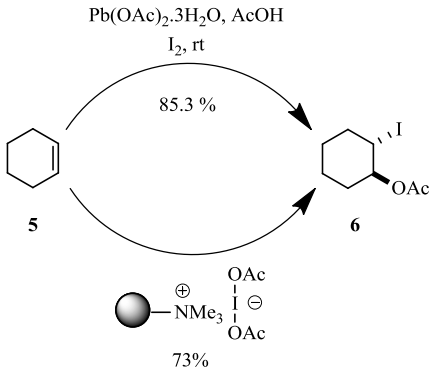
Organocatalysis is dominated by Lewis base catalysts. A variety of nitrogen compounds such as aliphatic amines,[11,12] heteroaromatic amines,[13] imides (e.g., NBS, NIS),[14] amides,[15] guanidines,[15] amidines[16] and sulfonamides[17] are excellent carrying agents for transferring electrophilic halogen to alkenes via intermediate halonium ions or a nitrogen-X^+-alkene complex.

In the last two decades, dramatic upsurge in methodologies for the racemic and enantioselective halofunctionalization reactions of functionalized and non-functionalized alkenes employing procedure catalytic in organocatalysts are reported in the literature. A brief historical background and recent advances in racemic and enantioselective inter- and intramolecular halofunctionalization reaction of alkenes will be reviewed in this chapter.

3.2 Intermolecular Halofunctionalization Reactions

Regio- and diastereoselective vicinal halofunctionalization of alkenes is one of the oldest reactions reported in the literature.[18] A variety of iodo functionalized compounds such as 2-iodoisocyanate,[19] 2-iodothiocyanate,[20] 2-iodonitrate,[19] 2-iodoazide,[21] 2-iodocarboxylate,[22] and 2-iodonitrone[23] were diastereoselectivity synthesized from the regioselective openings of iodonium ion intermediates with SCN^-, CN^-, NO_2^-, N_3^-, $RCOO^-$, $R_1R_2C{=}NR_3^+O^-$ nucleophiles respectively.[24] 2-Iodoacetate can be synthesized by the reaction of alkenes with $I_2/Cu(OAc)_2$, NIS/AcOH or $I_2/Pb(OAc)_2$ systems.[24] Kirschning and co-worker[25] employed polymer-supported di(acyloxy)-halogenate (I) complexes for the regioselective bromo/iodoacetoxylation of cyclic and acyclic alkenes (**Scheme 3.2**).

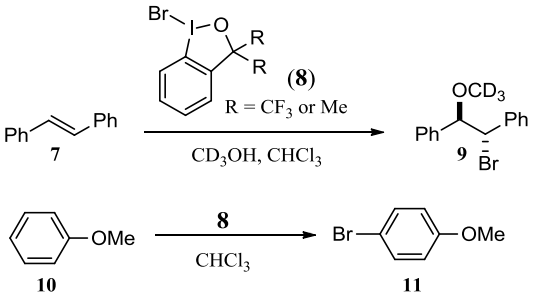
Scheme 3.2 Iodoacetoxylation Reactions of Cyclohexene.[24, 25]



In 2006, Braddock and cowokers[26, 27] reported the bromoetherification reaction of *trans*-stilbene **7** using bromoiodinane **8** [synthesized in situ from the reaction of 2-(2-iodo-phenyl)-propan-2-ol with *N*-bromosuccinimide (NBS)] as a source of electrophilic bromine (**Scheme 3.3**). The identity of I(III)–Br bond was confirmed by single crystal X-ray crystallography. The stoichiometric amount of bromoiodinane **8** was also used for the *para*-bromination of anisole. The effectiveness

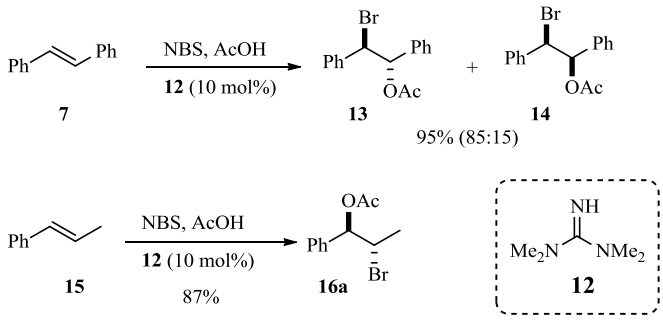
of the bromoiodinane used for the reactions was enhanced by increasing the nucleophilicity of the *ortho* substituent. The authors claimed the involvements of iodine in relatively rare I (I) and I (III) oxidation state in the reactions. This result uncovered the new avenue for the enantioselective bromination of prochiral olefin and was recently used by Borhan groups[28] for the bromolactonization reactions of unsaturated acids.

Scheme 3.3 Bromoiodinane **8** Promoted Bromofuntionalization Reaction.[26, 27]



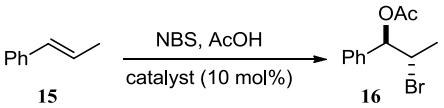
In the continued investigation for designing new organocatalyst for halofunctionalization reaction of alkenes, Braddock and coworkers also explored *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide and tetramethyl guanidine as potent catalysts for efficient bromoacetoxylation reaction of non-functionalized alkenes using *N*-bromosuccinimide as brominating agent (**Scheme 3.4**).[15] During their investigation, tetramethyl guanidine **12** displayed the best catalytic activity among the screened amides and guanidines catalysts affording high yields and diastereoselectivities of bromofunctionalized products.[15,16]

Scheme 3.4 Amide and Guanidine Catalyzed Bromoacetoxylation Reactions of *trans*-Stilbene and *trans-β*-methylstyrene.[15]



Later on, the same group also reported amidines **17-19** catalyzed bromoacetoxylation reaction of alkenes (**Scheme 3.5**).[16] Syntheses and utilization of racemic *iso*-amarine (**17**) as organocatalyst for the bromoacetoxylation reaction of alkenes showed that catalyst loading as low as 1 mol% was sufficient for affording excellent yields and diastereoselectivity. The intermediacy of *N*-bromoamidinium ion in the reaction was confirmed by the isolation of the crystals and their X-ray crystallographic studies. On the other hand, attempted efforts to control enantioselectivity in bromoacetoxylation reactions of *trans-β*-methyl styrene with NBS using chiral (*R*,*R*)-*iso*-amarine (**17**), chiral [2.2] paracyclophane amidine (**18**) or C_3-symmetric amidine (**19**) failed.

Scheme 3.5 Bromoacetoxylation Reaction of *trans*-*β*-Methylstyrene.[16]

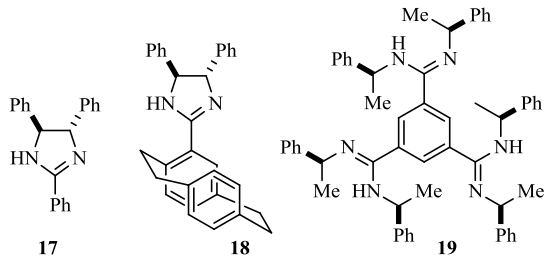


15 **16**

racemic **17** rt (1 h) 91%

chiral **18** -78 °C (28 h) 5%, 0% ee

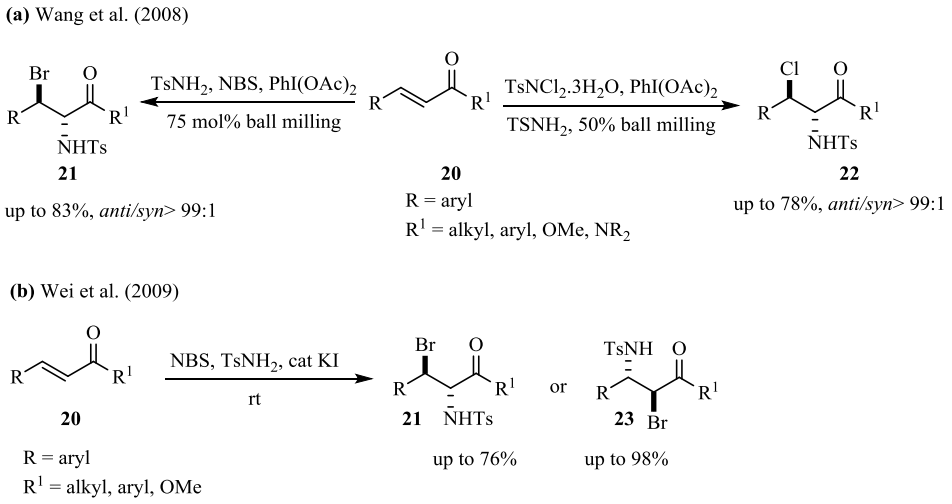
chiral **19** -78 °C (28 h) 45%, 0% ee



17 **18** **19**

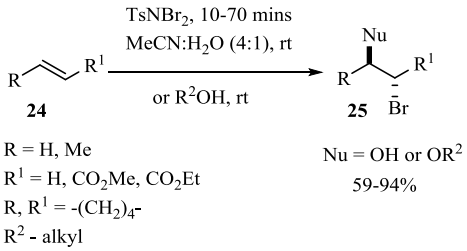
Li and co-workers[29] reported the transition metal catalyzed haloamination reaction of *α,β*-unsaturated esters, and *α,β*-unsaturated ketones using *N*-halo sources in ionic solvents (**Scheme 3.6, a**). The protocol was also successfully extended to haloamination reactions of *α,β*-unsaturated oxazolidinones[30, 31] in ionic solvents; both in the presence or absence of transition metal catalyst. One of the major limitations of the curerent method was the involvement of highly expensive ionic solvent for the reaction which increases the cost of haloamination product during industrial scale syntheses. A regio- and diastereoselective haloamination (e.g., halogen = Cl, Br) of *α,β*-unsaturated esters, ketones and amides was also achieved by using catalytic amounts of hypervalent iodine [$PhI(OAc)_2$][32] and potassium iodide (**Scheme 3.6, b**).[33] The intermediacy of halonium ion in the presence of catalytic system was proposed in all of these reactions.

Scheme 3.6 Haloamination Reactions of *α,β*-Unsaturated Ketones, Esters and Amides.[29, 33]



The vicinal halohydrins and haloethers are highly attractive structural subunits of bioactive natural products.[34] Generally, vicinal halohydrins are synthesized by the regioselective opening of chiral epoxides with hydrogen halide.[35] However, significant amounts of vicinal-dihalides by-products formation limited their uses in the reaction. Vicinal halohydrin can also be synthesized from the reaction of alkenes with *N*-halosuccinimide in an ionic solvent [i.e., 1-butyl-3-methylimidazolium tetrafluoroborate ((bmim)BF_4)].[36] Although, this method gives bromo- and iodohydrins in excellent yield, it indeed needs highly expensive ionic solvent for the reaction. A regioselective method for the conversion of electron rich and electron deficient alkenes to the corresponding vicinal bromohydrins and alkoxybromides using *N*,*N*-dibromo-*p*-toluenesulfonamide as brominating agent in the absence of a catalyst was recently reported (**Scheme 3.7**).[17] These reactions gave bromohydrin products in moderate to excellent yields in the absence of catalytic systems.

Scheme 3.7 Vicinal Halohydrin Formation of Alkene.[17]



Although all of these methodologies significantly elaborated the field of racemic halofunctionalization reactions by the use of new reagents and/or catalytic procedure, none of the existing methodologies are successful for enantioselective vicinal halofunctionalization reaction of alkenes.

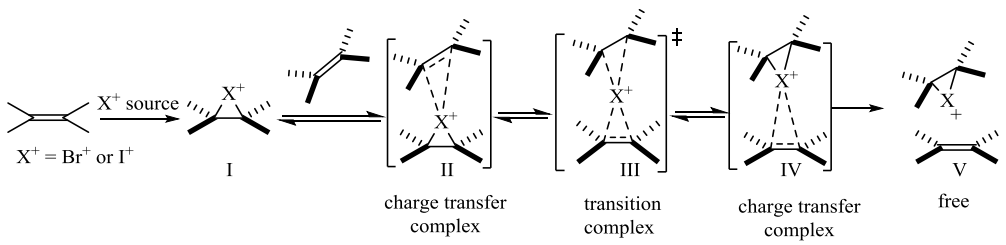
3.21 Enantioselective Halofunctionalization Reactions

The development of new methodologies for regio- and stereoselective functionalization reaction of alkenes has seen fresh impetus in recent years. Although, ample examples on enantioselective epoxidation,[37, 38] aziridination,[38] dihydroxylation,[39] aminohydroxylation,[40] and hydroboration[41] reaction of alkenes and their mechanistic and kinetic profile for heteroatom functionalization exist in the literature, the chemistry of enantioselective halofunctionalization reaction of alkenes was quite less explored.

The enantioselective halofunctionalization reactions of alkenes via halonium ion intermediates depend upon several factors including the substrate structure, catalyst, solvent, and reaction temperature. The halofunctionalization reactions precede via halonium ion transfer from alkenes to alkenes usually diminished the enantioselectivity as confirmed by Brown and

coworker's ^{1}H-NMR, ^{13}C-NMR and X-ray diffraction studied. This was further supported by computational study using Density Functional Theory (DFT) calculations of bromo/iodonium ion complex of adamantylidine adamantine.[13, 42] The model system shown in **Scheme 3.8** can be used to rationalize results. In this model, the approach of halonium ion to the second molecule of alkene give a reversible charge transfer complex II also called π-complex. This π-complex is in equilibrium with a second charge transfer complex IV via transition state III. The transfer of X^+ ion from the first alkene molecule to second one deliver the second halonium ion intermediate with the release of first alkene molecule. The *ab initio* calculation of the transition state showed that the bromonium ion exchange between two degenerate charge transfer complexes II and IV was -4.2 kcal/mol lower in energy than the corresponding starting materials while the transition state complex III had 9.3 kcal/mol higher in energy than that of the reactants. On the other hand, degenerate charge transfer complexes II and IV and transition state complex III of iodonium ion intermediate had -4.7 and 1.9 kcal/mol energies relative to the reactants respectively. These DFT results confirmed the necessity of asymmetric catalysts that can prevent or lower such alkene-alkene halonium ion transfer process in order to promote enantioselective halofunctionalization reactions. Hence, a chemical process where the rate of halonium ion transfers from alkene to alkene is slower than the collapse of halonium ion intermediate is desired for acheiving enantioenriched product.

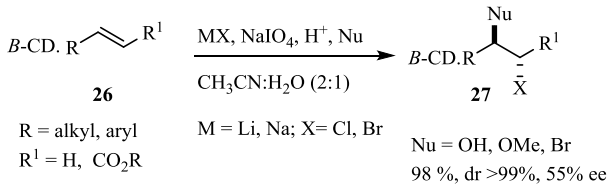
Scheme 3.8 Alkene to Alkene Bromo/iodonium Ion Transfer Mechanism.[42]



The second and main problem associated with enantioselective halo-functionalization reactions is the choice of the asymmetric catalyst that discriminate the *re* or *si* face of the C=C bonds during halonium ion formation. An asymmetric catalyst that can selectively locked the transition state of an alkene-halonium ion complex in a definite conformation and blocked one face of halonium ion complex is essential for high enantioselectivity. The nucleophilic attack on the halonium ion intermediates selectively from the less hindered face give enantioenriched halofunctionalized product. The third major problem involved controlling the background reactions which usually give racemic products. Besides, the position of the chiral center in asymmetric catalyst or *N*-halonium ion sources also affects the enantioselectivity of the pathway.

In 2003, Sudalai and coworkers reported the first substrate controlled intermolecular enantioselective bromohydroxylation reaction of *β*-cyclodextrin (*β*-CD)-alkene complex **26** using sodium or lithium salts [NaX/LiX (X = Cl, Br)] as halogenating agents and sodium periodate ($NaIO_4$) as oxidizing agents (**Scheme 3.9**). This reaction gave halofunctionalized product **27** in excellent yields, regio- and diastereoselectivity but with moderate enantioselectivity (98%, dr >99%, 55% ee).[43]

Scheme 3.9 Enantioselective Bromination of *β*-Cyclodextrin (*β*-CD)-alkene Complex.[43]

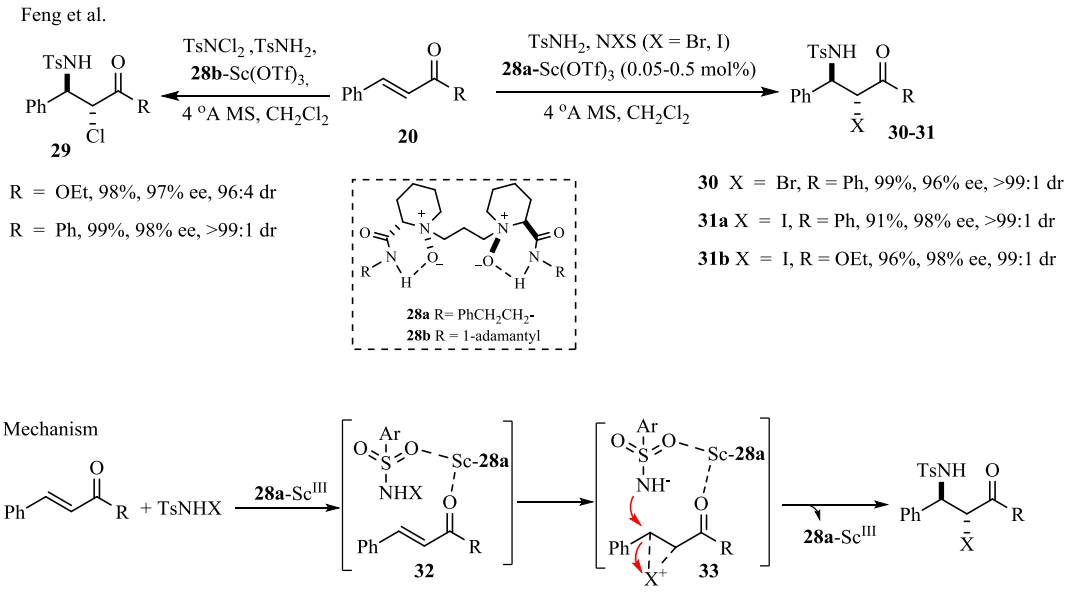


In 2010, Feng and coworkers[44] reported the first breakthrough in reagent controlled enantioselective bromoamination reaction of chalcone employing catalytic amounts of chiral transition metal complexes [i.e., (*S*)-pipecolic acid derived *N*,*N*'-dioxide (**28**)-$Sc(OTf)_3$, **Scheme**

3.10]. Although, the previous methods for the bromoamination of chalcone proceed through aziridinium ion intermediates which upon reaction with bromide anion gave α-bromo-*β*-amino ketones, the **28**-$Sc(OTf)_3$ catalyzed bromoamination of chalcone gave *α*-amino-*β*-bromo ketones. The involvement of bromonium ion intermediate was proposed in the Sc(III) catalyzed reaction. In this reaction, Sc(III) complexes acted as a Lewis acid and activated both the nucleophilic and electrophilic substrate by coordination with sulfonyl and carbonyl functional groups respectively. The bromoamination reaction of chalcone with *p*-toluenesulfonamide ($TsNH_2$) and *N*-bromosuccinimide (NBS) in the presence of **28**-$Sc(OTf)_3$ and 4 Å molecular sieves gave the *α*-bromo-*β*-amino ketone with 99% yield, 99:1 dr and 99% ee under optimized reaction conditions. Enantioselectivity in the bromoamination product **30**-**31** is depended upon several factors. Usually, the presence of water diminished the yields and enantioselectivity probably due to deterioration of the catalytic activity. This shortcoming was overcome by the use of 4 Å molecular sieves. Besides, dichloromethane was explored as the best solvent for achieving high yields and enantioselectivity. The employment of catalytic protocol for the enantioselective iodoamination reaction of chalcone and *α,β*-unsaturated-*γ*-keto esters also gave similar yields and enantioselectivity (38-98%, 92-99% ees).[45] To the contrary, chloroamination of chalcone using $NCS/TsNH_2$ reagents furnished low yield and poor enantioselectivity under identical reaction conditions. Modification of procedures using more active chlorine and nitrogen sources (i.e., $TsNCl_2/TsNH_2$) gave *α*-chloro-*β*-amino ketone in excellent yields and enantioselectivities (i.e., up to 99% yield and 99% ee). In addition, yield and enantioselectivity was comparable for chloroamination of *α,β*-unsaturated-*γ*-keto esters.[46] The observed stereochemical outcome of the reaction was rationalized by the mechanism where the reaction of chalcone and TsNHX with chiral *N*,*N*'-dioxide (**28**)-$Sc(OTf)_3$ catalyst give an association complex **32**. The enantioselective transfered of X^+ ion to the alkene via association complex **32** lead to halonium ion intermediates

33. The S_N2 opening of halonium ion by the incumbent nucleophile give the α-halo-β-amino ketones **29-31** with the subsequent regeneration of chiral Sc(III) catalyst.

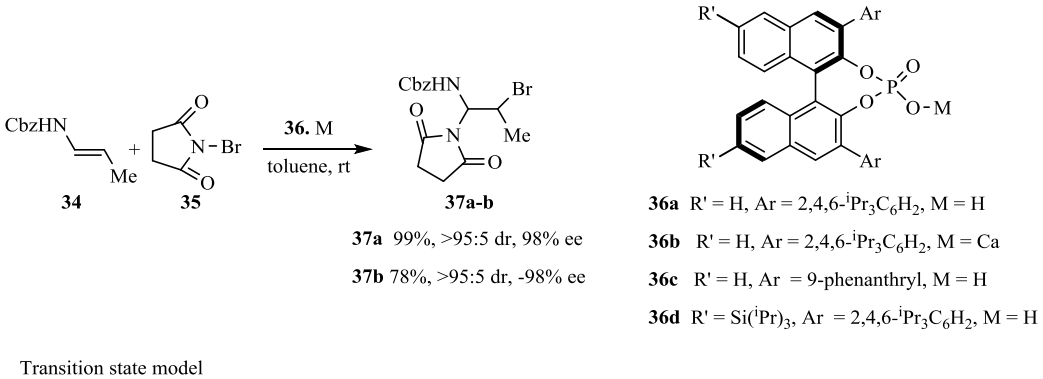
Scheme 3.10 Enantioselective Haloamination of Chalcone and Encarbamates.[44]



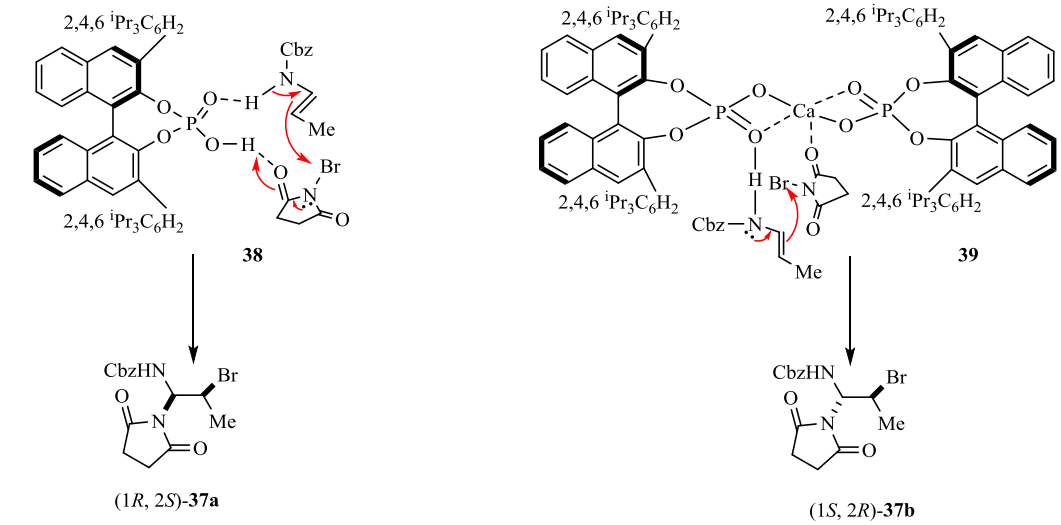
Recently, Masson and coworkers[47] explored a new method where chiral phosphoric acids and the corresponding calcium salts formed an ion pair complex with reacting species and catalyzed the bromoamination reaction of enecarbamates with high enantioselectivity (**Scheme 3.11**). The bromoamination reaction of *O*-benzyl-*N*-(*E*)-prop-1-en-1-yl carbamate **34** with NBS was promoted by catalytic amounts of bi-functional catalyst [i.e., (*R*)-3,3'-*bis*(2,4,6-triisopropylphenyl)-BINOL (TRIP) phosphoric acid, **36a** (1 mol %)] and afforded **37a** up to 99% yield, >95:5 dr and 98% ee under optimized reaction conditions. In this reaction, bi-functional catalysts acted as chelating ligands for activating both enecarbamates and NBS and promoted the bromoamination reaction. Interestingly, the use of catalytic amounts of the calcium or lithium

salts of the chiral phosphorus catalyst **36b** (1 mol %) gave other enantiomer (1*S*, 2*R*-**37a**) in good yields, diastereo- and enantioselectivity (up to 78% yield, >95:5 dr and 98% ee).

Scheme 3.11 (*R*)-BINOL Phorsphoric Acid Catalyzed Enantioselective Bromoamination of Enecarbamate **34**.[47]



Transition state model

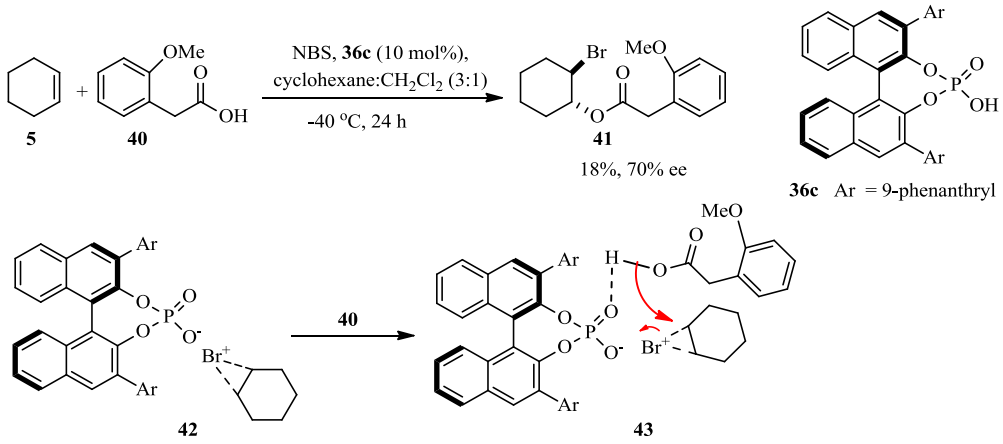


Although, the precise insight for the outcome of two enantiomers was not fully understood, the formation of **37a** (1*R*, 2*S*) was expected with the activation of NBS and encarbamate via hydrogen bonding as shown in TS **38** while the formation of **37b** (1*S*, 2*R*) was expected from the activation of NBS and encarbamate via metal chelation model **39**. The presence of highly

hindered 2,4,6-$^{i}Pr_3C_6H_2$ blocked the *Re* face of the NBS in TS **38** thereby *Si* attack lead to (*S*)-imine intermediate. To the contrary, *Re*-face of calcium bis(phosphate) was fully accessible for the attack in TS **39** and that TS lead to *R* isomer. The highly diastereoselective nucleophilic attack of the imide to (*S*)- or (*R*)- imine afforded the final **37a** (1*R*, 2*S*) or **37b** (1*S*, 2*R*) bromoaminal products respectively. The synthetic versatility of the methodology was illustrated by their successful applications for syntheses of chiral aziridine,[48] imidazolidine-2-ones[48] and pyrrolizidines[49] units presents in several natural products.

Although Braddock and co-workers attempted intermolecular enantioselective haloacetoxylation reactions of *β*-methylstyrene with NBS and acetic acid in the presence of [2.2] paracyclophane amidite failed (*vide supra,* **Scheme 3.5**).[16] Enantioselective bromoesterification of cyclohexene catalyzed by a Lewis base (e.g., 2-aminopyridine and cinchona alkaloids base) and Brønsted acid (e.g., 9-phenanthryl substituted chiral phosphoric acid) was reported by Li and coworkers very recently (**Scheme 3.12**).[50] The screening of several solvents, *N*-halo derivatives, acid derivatives and aryl substituted chiral phosphoric acid catalysts showed that the best enantioselectivity was observed while using arylacetic acid **40** and NBS with cyclohexene in the presence of chiral phosphoric acid catalyst **36c** (18%, 70% ee). The authors proposed a model for the involvement of new ion pair complex **43** during the reaction of chiral BINOL-based phosphate **36c** with the bromonium ion intermediate. A competitive background reaction involved opening of bromonium ion intermediate **43** by chiral phosphate anion or carboxylic acid was proposed for the diminished yield of the reaction.

Scheme 3.12 Enantioselective Bromoacetoxylation Reaction of Cyclohexene.[50]



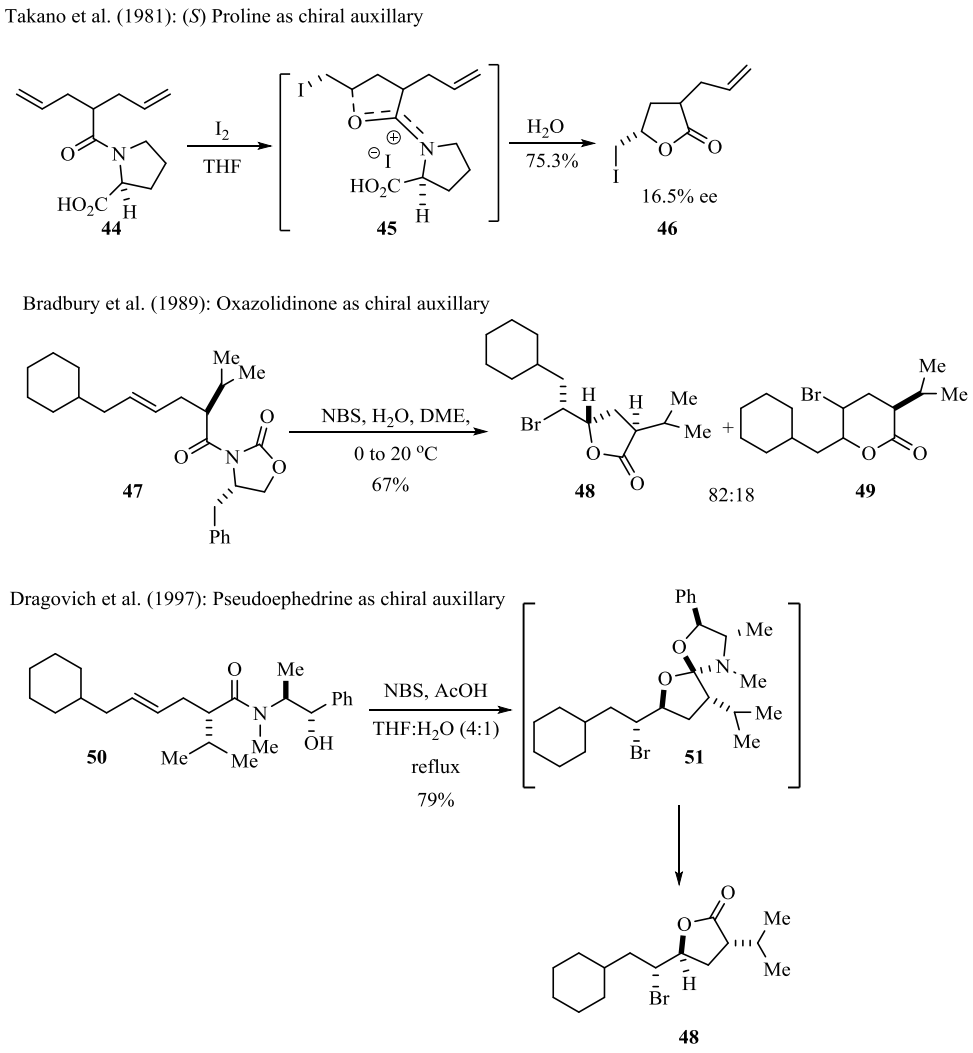
3.3 Intramolecular Halofunctionalization Reactions

3.31 Halolactonization

The chemistry of halolactonization reaction of unsaturated acids is quite old as Fittig[51] reported the first bromolactonization reactions in 1883. The iodine variant of halolactonization reaction was reported by Bougault[52] in 1908 using potassium iodide as oxidant while the chlorolactonization reaction was first reported by Bloomfield[53] in 1932. Since then, halogen (halogen = Br or I) promoted lactonization of unsaturated acids is a fundamental method for the syntheses of medium sized halolactones in organic chemistry.[54,92] The mechanism of halolactonization reaction involves the formation of a halonium ion intermediate in the first step which undergoes intramolecular nucleophilic opening to form the cyclic product during the final step.

Despite ample examples on racemic halolactonization reaction of unsaturated acids, the chemistry of corresponding enantiocontrolled halolactonization reaction is significantly less explored. Enantioselective halolactonization reactions are of two kinds namely "substrate controlled" and "reagent controlled" halolactonization reactions. In substrate controlled reaction, a pendant chiral moiety present in the substrate control the chirality of the newly generated stereogenic center via steric effect while a chiral catalyst or chiral reagent facially discriminates *re* or *si* faces of halonium ion intermediates and controls the enantioselectivity in reagent controlled halolactonization reaction. The chemistry of "substrate controlled enantioselective halolactonization" reaction using chiral auxiliary is more widely explored than the reagent controlled ones. Tanako and coworkers[55] reported the first substrate controlled iodolactonization homoallylic acid **44** with molecular iodine where pendent proline in the substrate was used as a chiral auxiallry. The reaction gave iodolactone **46** in low enantioselectivity (16.5% ee, **Scheme 3.13**). Subsequently, chiral oxazolidinones **47**[56] and pseudoephedrine-based amide **50**[57] were successfully employed as chiral auxiliaries in halolactonization reactions.

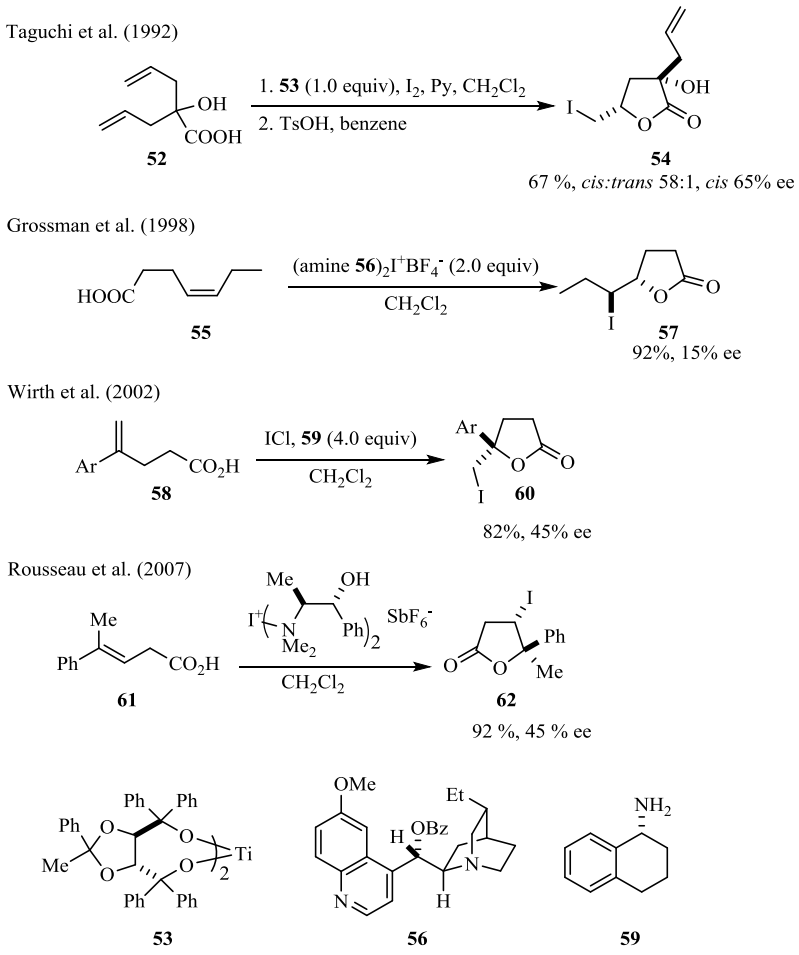
Scheme 3.13 Substrate Controlled Enantioselective Halolactonization Reactions.[55-57]



A large number of transition metal complexes and organocatalysts are used for the reagents controlled enantioselective halolactonization reactions (**Scheme 3.14**). Taguchi and coworkers[58] reported the first reagent controlled enantioselective iodolactonization reaction of 2-allylic-2-hydroxy-4-pentenoic acid (**52**) catalyzed by chiral titanium complex **53** affording iodolactone **54** in good yield and moderate enantioselectivity (67%, 65% ee). Grossman[59] reported the first reagent controlled enantioselective iodolactonization reactions of **55** using chiral

dihydroquinidine (**56**)-iodine complex as organocatalyst affording **57** in high yields but with poor enantioselectivity (92%, 15% ee). Subsequently, iodolactonization reaction of 4-aryl-4-pentenoic acid (**58**) catalyzed by chiral amine **59**[12] and bromo- or iodolactonization of 4-aryl substituted 4-pentenoic acid (**61**) using iodo-*bis*-(*N*-methylephedrine)-hexafluoroantimoniate[60] were explored. In both of these reactions, good yields of iodolactone were observed despite modest enantioselectivity. However authors failed to provide detailed mechanistic insight for the observed enantioselectivity in both of these reactions.

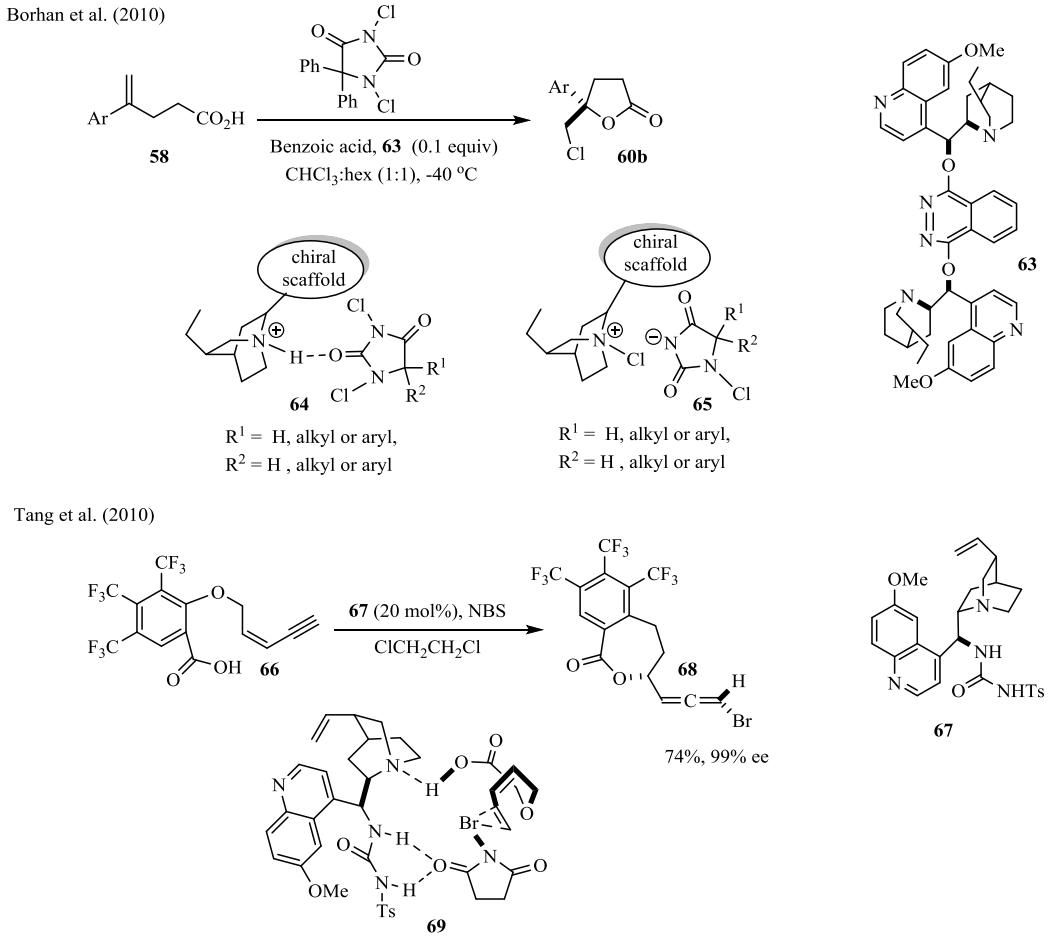
Scheme 3.14 Reagent Controlled Enantioselective Halolactonization Reactions.[58-60]



The big breakthrough in reagent controlled halolactonization reactions occurred in 2010 when Borhan and coworkers[61,62] reported $(DHQD)_2PHAL$ (**63**) catalyzed enantioselective chlorolactonization reaction of 4-aryl-4-pentenoic acid **58** with 1,3-dichloro-5,5-diphenylhydantoin affording chlorolactone **60b** in excellent yield and good enantioselectivity (up to 99% yields, up to 90% ee, **Scheme 3.15**). In their study, authors claimed that a close association of chlorohydantoin with quinuclidine part of $(DHQD)_2PHAL$ was responsible for the high asymmetric induction in the product. A series of controlled experiments confirmed that the presences of sterically hindered group at C5 position of chlorohydantoin enhanced the enantioselectivity. Besides, a complex of 1,3-dichlorohydantoin with $(DHQD)_2PHAL$ was characterized by their ^{1}H-NMR study. Based on these results, formation of two different kinds of association complexes were proposed in the chlorolactonization reactions. In the first kind (i.e., **64**), an intermolecular hydrogen bonding between the 1,3-dichlorohydantoin and the protonated $(DHQD)_2PHAL$ was proposed. The second model involved the formation of chloroquinuclidinium salts via the transfer of Cl^+ to the $(DHQD)_2PHAL$ and thereby generated an association complex **65**. The participation of first complex **64** was rationalized due to the necessity of Brønsted acid as an additive for the chlorolactonization reactions while the involvement was second complex **65** was proposed due to the successful halocyclization of unsaturated amides even in the absence of Brønsted acid. In a mean time, Tang and co-workers[63] reported the cinchona alkaloids **67** catalyzed enantioselective bromolactonization reactions of conjugated *Z*-enynes **66** using NBS as bromonium ion source. In this reaction, bifunctional catalyst **67** activated the NBS via hydrogen bonding while the quinucidine moiety was hydrogen bonded with acidic hydrogen and gave association complex **69**. The close association complexes between Brønsted acid and base was confirmed by their control experiments where standing the

mixture of catalyst **67** (0.2 equiv) with NBS (1.2 equiv) for 20 minutes before employing for the reaction diminished the enantioselectivity (from 95:5 to 77:23).

Scheme 3.15 Enantioselective Halolactonization Reaction of **58** and **66**.[61-63]

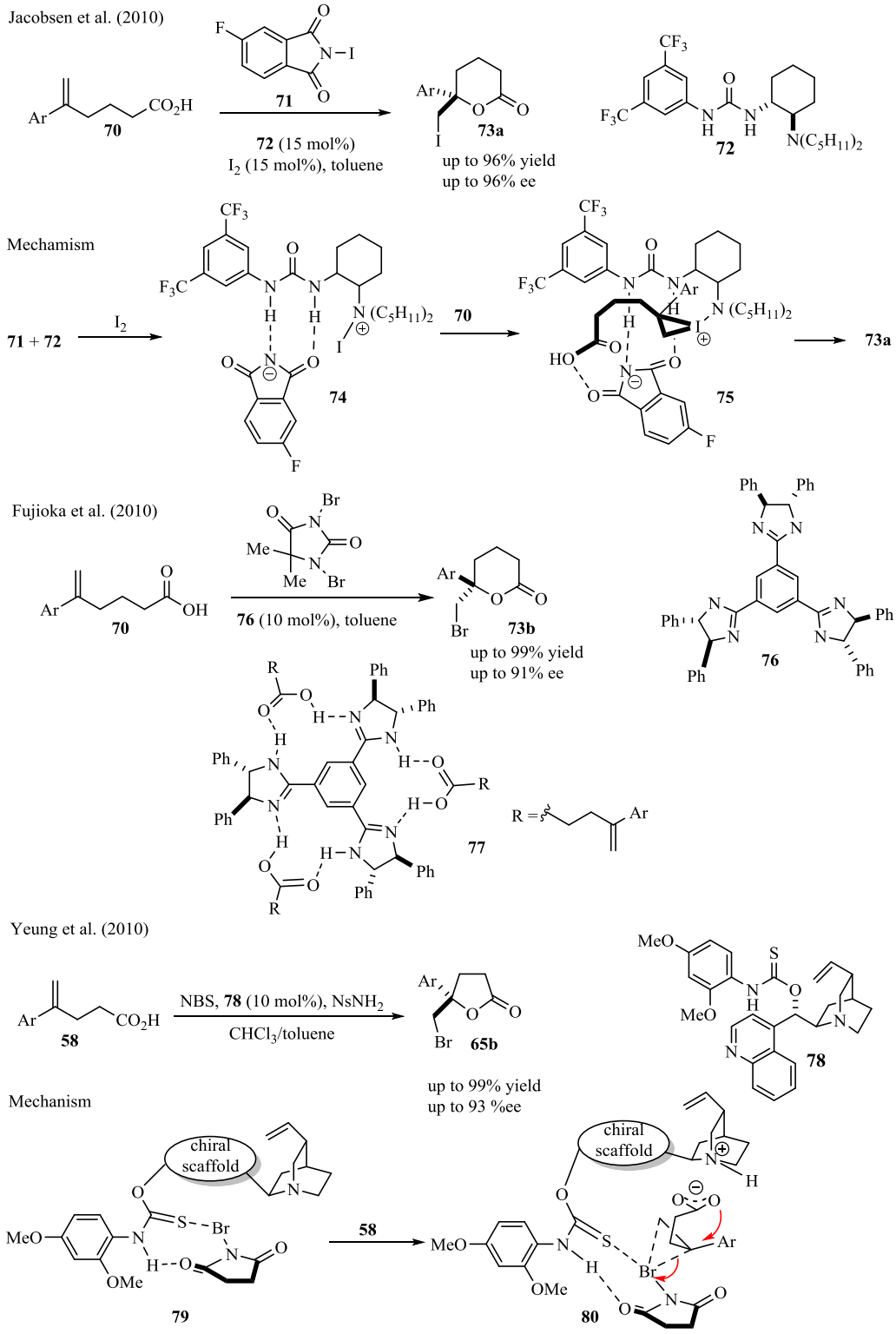


Subsequently, Veitch and Jacobson[64] reported bifunctional tertiary aminourea derivative **72** catalyzed enantioselective iodolactonization reactions of conjugated and unconjugated alkenoic acids using *N*-iodofluoropthalimide **71** as an iodonium ion source. The author claimed that the use of catalytic amounts of molecular iodine (15 mol%) in the presence of protic acid activated *N*-iodofluoropthalimide and the newly formed triiodide cation **74** was involved in the

iodolactonization reaction. The authors also claimed that bifunctional tertiary aminourea catalyst **72** acted as a Lewis base and activated the *N*-iodofluoropthalimide by H-bonding and gave intermediate **74**. The resulting iodoaminium ion **74** next transferred I^+ ion to the alkene followed by simultaneous activation of the substrate via the deprotonation of acidic hydrogen by succinamide carbonyls gave TS **75**. Subsequent cyclization of intermediate **75** in the rate and enantio-determining step delivered the final product **73a**. Fujioka and coworkers[65] also reported C_3-symmetric chiral trisimidazoline **76** catalyzed enantioselective bromolactonization reaction of 1,1-disubstituted, trisubstituted and tetrasubstitued alkenes using bromohydantoin as bromonium ion source. The authors claimed that the intermediacy of ion pair complex **77** during the reaction was responsible for creating the chiral environment in the observed product.

In addition to the nitrogen based organocatalysts, the sulfur based organocatalyst showed their effectiveness for the halolactonization reactions. Yeung and coworkers[66] reported the chiral aminothiocarbamate **78** catalyzed enantioselective bromolactonization reaction of 4-phenyl-4-pentenoic acid **58** using NBS as bromonium ion source. Attempted screening of several sulfur based catalyst showed that thiocarbamate catalyst **78** was highly versatile for the bromolactonization reaction. Attempted modification of catalyst by replacing S with O or N-H with N-Me or replacing thiocarbamate with thiourea moiety diminished the yield and enantioselectivity of the bromolactones confirming the involvement of both S and N-H for the enantioselectivity and reactivity. Based on these results, a transition state model for the dual activation of NBS with thiocarbamate was proposed. In this model, the reaction of thiocarbamate **78** with NBS formed an activated complex **79** which on reaction with alkenyl acid gave transition state **80**. The electron rich 2,4-dimethoxyphenyl ring in the highly rigid ionized complex **80** next acted as a steric screening group and controlled the activity of thiocarbamate's N-H and promoted the asymmetric induction by suppressing the alkene-alkene halogen exchange reaction. The

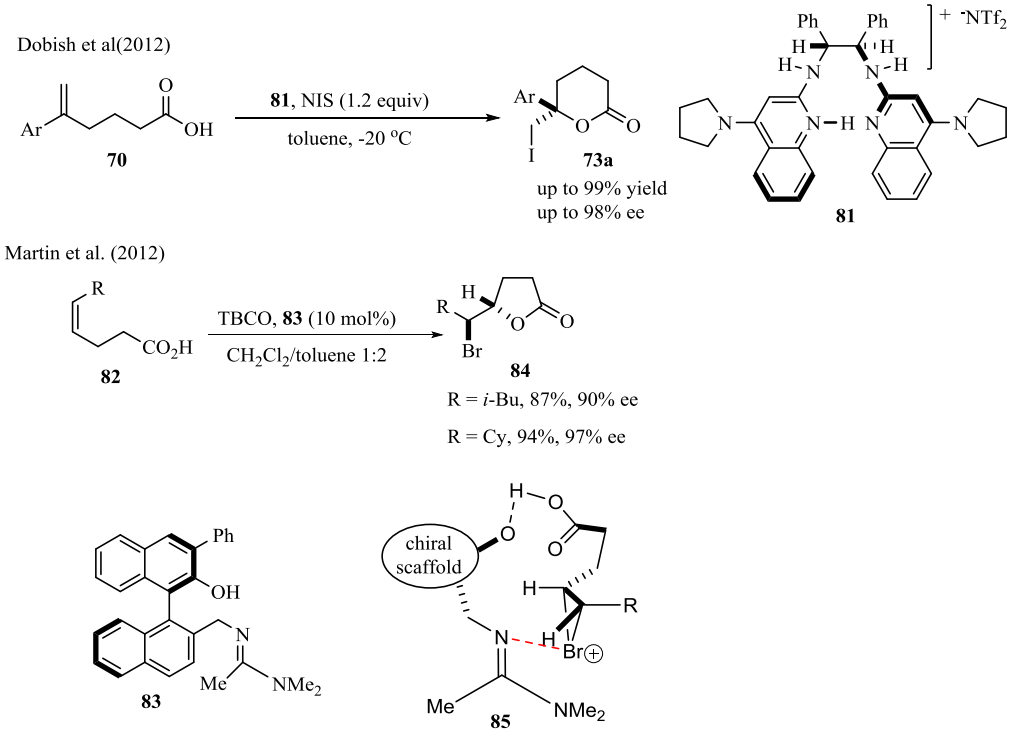
Scheme 3.16 Enantioselective Halolactonization Reaction of **58** and **70**.[64-66]



versatility of the method was illustrated by their successful application for the syntheses of enatioenriched δ-lactone[67] and 3,4-dihydroisocoumarin[68] derivatives.

Dobish and Johnston[69] employed a new concept where achiral counter ion controlled the enantioselectivity during the Brønsted acid catalyzed iodolactonization reactions of unsaturated acids. Authors claimed that the reaction of stilbenediamine-derived BAM with protic acid formed polar ionic hydrogen bonded complexes **81** (BAP-H^+) with achiral counter ion and that behaved as bifunctional catalyst and promoted the enantiocontrolled reactions. Although, authors failed to propose the mechanistic rationale for the enantiocontrolled process, an activation of NIS by acidic and activation of carboxylic acid part of **70** by basic part of bifunctional catalyst was invoked. Martin and coworkers[70] reported the enantioselective bromolactonization reactions of 5-aryl/alkyl substituted 4-pentenoic acid **82** using 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) as source of bromonium ion catalyzed by bifunctional BINOL-imine catalyst **83**. This method involved 5-*exo* mode of cyclization affording new carbon-bromine bonds at a stereogenic center with moderate to good enantioselectivity (70-97% ee). Screening of bromonium ion sources for the bromolactonization reaction showed that NBS and DBDMH were less effective under the condition where TBCO gave good yields and good enantioselectivity. In addition, the bromolactonization of *Z*-alkenes was promoted with higher enantiocontrolled fashion than that of corresponding *E*-alkenes. Authors claimed that the hydrogen bonding between the phenolic –OH with carboxyl group of the substrate oriented the substrate in a way to reduce the torsional strain between the substituent on the alkene and binaphthyl scaffold. The bromonium ion was expected to be stabilized by interaction with amidine moiety as shown in transition state **85**.

Scheme 3.17 Enantioselective Halolactonization Reaction of **70**, **82** and **86**.[69-71]



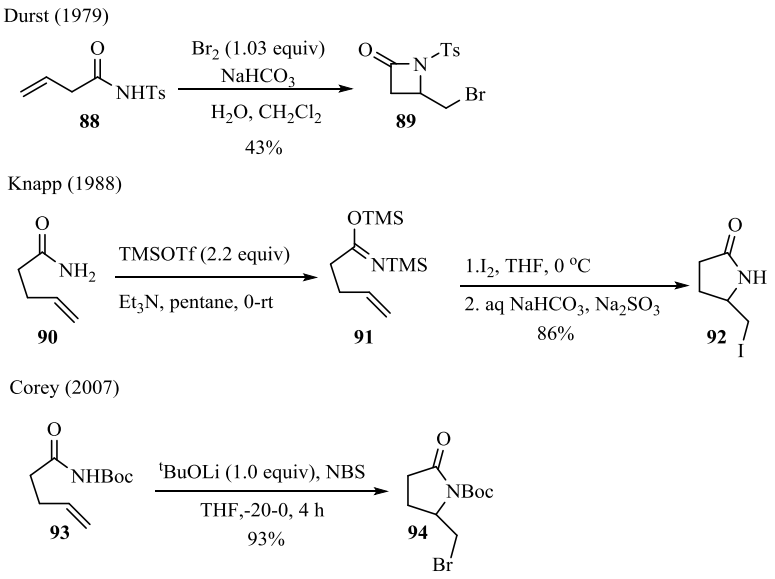
Very recently, Hennecke and co-workers[71] reported the $(DHQD)_2PHAL$ catalyzed enantioselective bromolactonization reaction of non-conjugated alkynoic acids **86** using NBS as brominating reagents. This newly developed methodology allowed the enantioselective syntheses of bromoenol lactones **87** bearing a tetrasubstituted alkene and an all-carbon quaternary stereocenter. The reaction was proceed via transition state **88** where acidic part in the substrate was activated by H-bonding with bridged *N*-atom while the bromonium ion was activated in coordination with quaternary ammonium nitrogen of chiral catalyst. The bromoenol lactone **87** has application for the syntheses of haloenol lactones which acted as covalent inhibitors of serine proteases in bioorganic chemistry. The recent finding in the enantioselective halolactonization reactions were summarized in several reviews.[4, 54, 72, 73]

3.32 Halolactamization

Halolactams, the nitrogen analog of halolactones are active constituent of several natural and pharmacological products.[74] One of the common methods for the syntheses of halolactam involved the reaction of unsaturated amides with halonium ion sources. However this methodology rather gives halolactone as a major product with minor amounts of halolactams.[75] For promoting the halolactamization reaction, the elevation of nitrogen nucleophilicity and diminution of oxygen nucleophilicity is essential. Bromolactam formation reaction of allyl amide **88** with molecular bromine in the presence of sodium bicarbonate ($NaHCO_3$) was the first example where nitrogen acts as nucleophile for the opening of bromonium ion intermediate in the presence of oxygen moiety.[76] This reaction however gave poor yield of bromolactam **88** (**Scheme 3.18**). Knapp and Leverse[77, 78] reported a modified procedure where unsaturated amine **90** was converted to the *N,O-bis*(trimethylsilyl) imidate intermediate **91** followed by reaction with

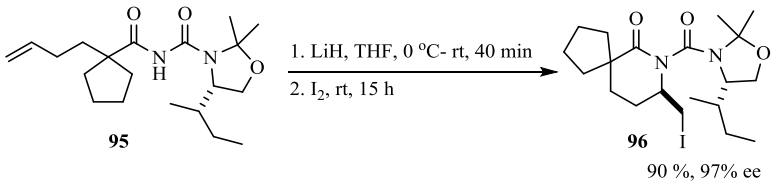
molecular iodine gave iodolactam **92** in good yields. The protection of both carbonyl oxygen and nitrogen atoms with trimethylsilyl groups enhances the nucleophilicity of nitrogen toward cyclization reaction. Subsequently, Corey and Yeung[79] reported the bromolactam formation reactions of *N*-Boc protected unsaturated amide **93** with NBS in the presence strong base ^{t}BuOLi which avoided the necessity of expensive and highly moisture sensitive trimethylsilyl triflate (TMSOTf) in the Knapp syntheses for the large scale syntheses of halolactam **94**. These results are summarized in several reviews.[54, 80]

Scheme 3.18 Halolactamization Reaction of Enamides.[76-79]



Li and coworker[81] reported the first and only example on substrate controlled enantioselective iodolactamization reaction of unsaturated amide with molecular iodine using (*4S*)-4-((*2R*)-2-butyl)-2,2-dimethyl-oxazolidineoxazolidine as chiral auxiliary (**Scheme 3.19**). The deprotonation of secondary amine with lithium hydride (LiH) followed by the attack of corresponding anions to the in situ generated iodonium ion intermediate gave iodolactam **96** in excellent yield and enantioselectivity (90%, 97% ee).

Scheme 3.19 Substrate Controlled Enantioselective Halocyclization of Enamide.[81]

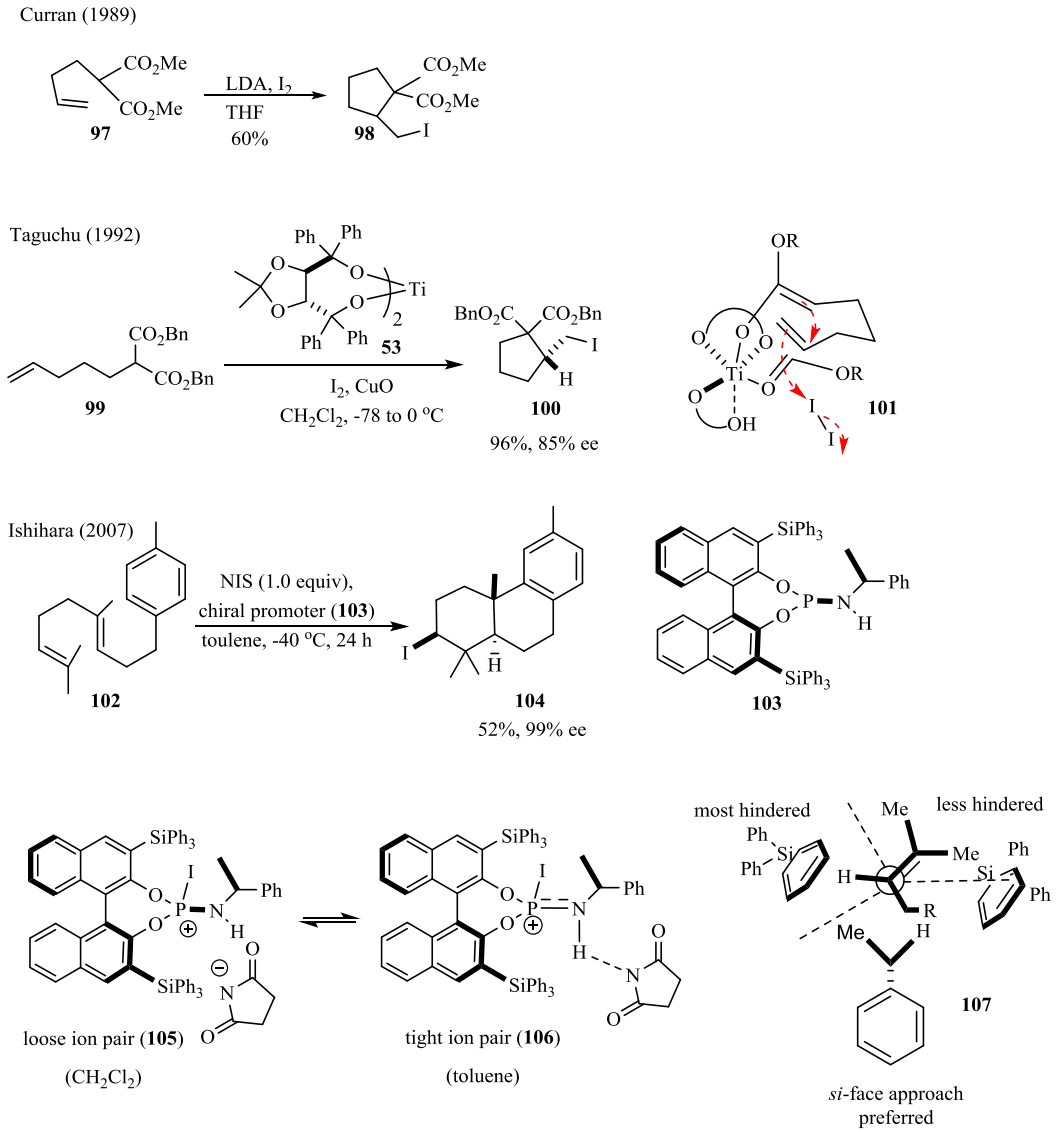


3.33 Halocyclization

The cyclic halogenated moieties are active constituents of several natural products and are abundantly isolated from marine species.[82] The biosynthesis of these compounds includes electrophilic halogenations of carbon carbon double bond. The first halocyclization reaction was reported by Curan and co-workers[83] during the reaction of dimethyl-4-pentenylmalonate **97** with molecular iodine in the presence of the strong base LDA (**Scheme 3.20**). After that, the chemistry of iodocyclization reaction was well explored. In 1992, Taguchi and coworkers[58] reported the titanium complexes **53** catalyzed enantioselective iodocyclization of dibenzyl-2-(4-pentenyl) malonate (**99**) with molecular iodine affording iodocyclopentane dibenzyl derivatives **100** in excellent yield and with good enantioselectivity (96%, 85% ee). In a chair like transition state **101**, the chiral ligand present in the titanium complex shielded one face of enolate hence the trans attack of enolate to the terminal olefin and molecular iodine gave the final product **100** with observed stereochemistry. In 2007 Ishihara and coworkers[3] reported an enantioselective halocyclization reaction of electron-rich homo(polyprenyl)arenes **102** using NXS (X= Br or I) and stoichiometric amounts of chiral phosphoramidite **103** affording iodoterpenoid **104** in moderate yield and excellent enantioselectivity (52%, up to 99% ee). The author claimed that the

activated iodiranium ion was formed in the reaction of NIS with phosphoramide and generated partial double bond character in P- N bond.

Scheme 3.20 Halocyclization Reactions of Olefinic Substrates.[3, 58, 83]



The formation of loose ionic species of phosphorium salts (i.e., **105**) in dichloromethane offer free rotation of the *N*-(1-phenylethyl) amino group on the P-N axis and that lead to no enantioselectivity. To the contrary, a tight ion pair where the hydrogen bonding between the

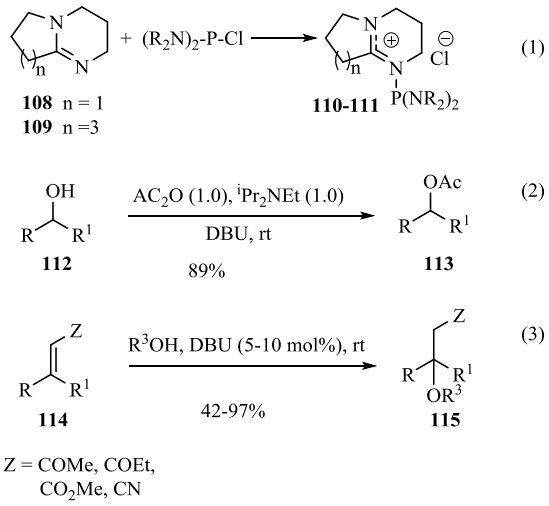
succinimide anion with N-H moiety of phosphorium salt in toluene (i.e., **106**) restricted the rotation of P-N bond and offer high enantioselectivity. As shown in TS **107**, the preferred *si*-face approach of the terminal isobutenyl group of the substrate to the activated iodine delivered the final product. The author claimed that the *re*- approach of the substrate was disfavored due to steric reason. More examples on catalytic and/or enantioselective polyene cyclizations promoted via halonium ion intermediate are summarized in a few reviews. [3, 54, 58,54]

In summary, organic chemists have utilized regio- and stereoselective electrophilic halofunctionalization reactions catalyzed by Lewis acids, Brønsted acids, Brønsted bases and phase transfer catalysts to produce a variety of natural products and synthetic intermediates.[4, 54] Although limited success in intermolecular enantioselective halofunctionalization of alkenes was achieved, especially in haloamination reactions,[44-46] the successful transformation of this protocol to intermolecular haloacetoxylation, haloetherification and other halo-functionalization reactions is still under development. The lack of chiral catalyst and alkene to alkene halonium ion transfer limits the enantioselective transformation from achiral alkene to chiral halo functionalized products. On the other hand, the chemistry of intramolecular enantioselective halofunctionalization reactions especially halolactonization,[10, 28, 61-66, 68-71] halolactamization,[80] and halocyclization[3, 58] is comparatively well explored in the last few years.

3.4 Amidines and Schiff Bases as Nucleophile and Nucleophilic Catalysts

1,5-Diazabicyclo-[4.3.0]-non-5-ene (DBN, **108**) and 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU, **109**) are highly versatile reagents that have broad applications as nucleophiles, nucleophilic catalysts or Lewis bases in organic syntheses. The nucleophilic substitution reaction of chlorophospane with amidines **108-109** give amidinium salts **110-111** (**Scheme 3.21**, eq 1)[84] while amidine **109** catalyzed acylation reaction of secondary alcohols (eq 2),[85] and conjugate addition of alcohol to α,β-unsaturated ketones, esters and nitriles (eq 3)[86] give corresponding product **115** in moderate to excellent yields. The synthetic versatility of these reagents are well explored and reported in several reviews[87, 88] and book chapters.[89]

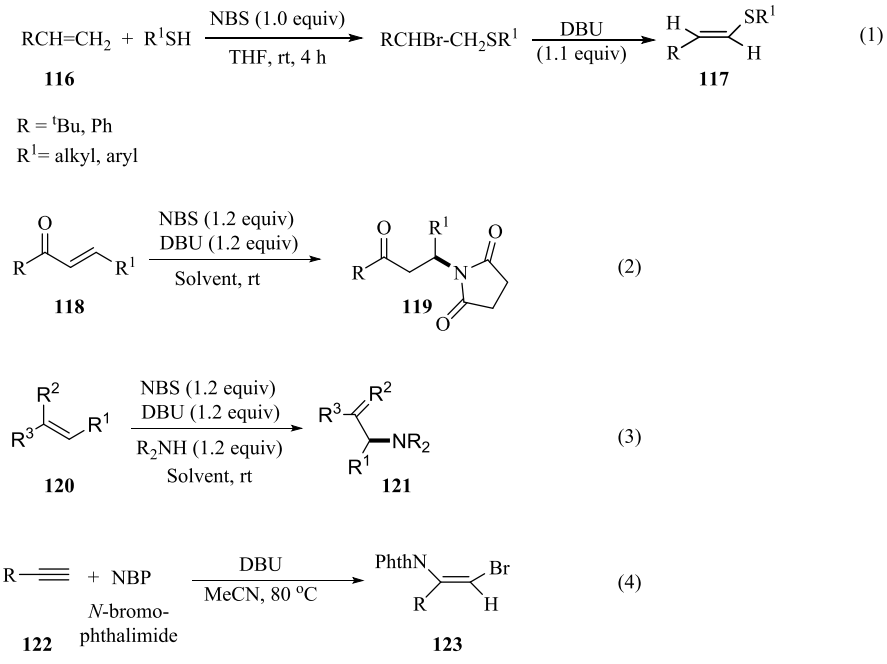
Scheme 3.21 Amidines as Nucleophile or Nucleophilic Catalyst. [84-86]



DBU also acted as a Lewis base in the alkenyl thioether syntheses.[90] The stereospecific reaction of styrene or *tert*-butylethylene **116** with alkyl or aryl thiols gives *E*-enol thioether **119**. The reaction proceeds via in situ addition-elimination mechanism and DBU acts as a Lewis base for the removal of hydrogen *β* to the bromine in the reaction (**Scheme 3.22,** eq 1). Wei and coworkers reported an unique examples of α-imidation of ketones[91] and tandem bromoamination

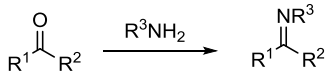
and debromination reactions of *α,β*-unsaturated enones[92] using stoichiometric each of DBU and *N*-bromoimide (eq 2). However the reaction failed with catalytic amounts of DBU. In these examples, *N*-bromoimide acts as the source of electrophilic bromine and nucleophilic nitrogen sources where as DBU acts as a nucleophilic reagent to activate the N-bromoimide as well as Lewis base for the removal of bromine from α-bromoketones. The same group also reported the *N*-bromoimide/DBU combination for the intramolecular allylic amination reactions of several alkenes (eq 3).[93] *N*-bromoimide/DBUsequence was also successfully extended for the bromo/chloroamination reactions of alkynes[94] very recently (eq 4). The newly discovered methodologies provide opportunities for the installation of amine functionality to the alkene and alkyne substrate under mild conditions.

Scheme 3.22 Synthetic Application of Amidines as Lewis Base. [90-94]



Schiff bases are the carbonyl analogs of nitrogen bearing C=N moiety and can be prepared by the condensation of aldehydes or ketones with primary amines with the release of water as the by-product of the reaction (**Scheme 3.23**). Schiff bases are environmentally friendly and can be prepared in low cost.

Scheme 3.23 General Method for the Synthesis of Schiff Base.



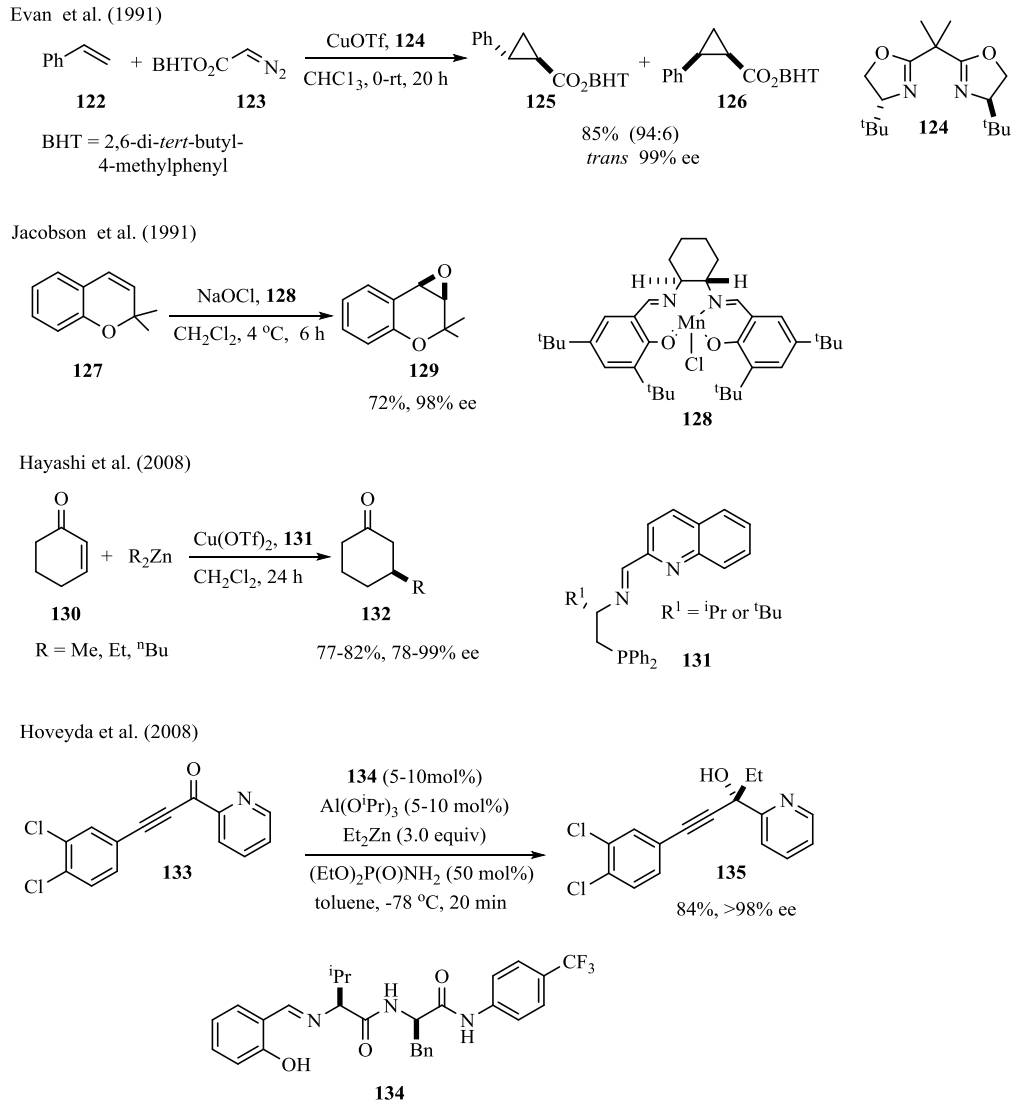
R^1, R^3 = alkyl or aryl
R^2 = H, alkyl or aryl

Schiff bases catalyze large numbers of organic reactions.[95-97] The highly chelating nature of Schiff base via nitrogen atom results their abundant use in the transition metal catalyzed reactions. Evans and coworkers[98] reported the copper(I) salt and bis(oxazoline) catalyzed enantioselective cyclopropanation reactions of mono and disubstituted alkenes (**Scheme 3.24**). The reaction of styrene with diazo-2,6-di-*tert*-butyl-4-methylphenyl carbonate in the presence of catalytic amounts of copper triflate and chiral bis(oxazoline) **124** gave *trans*-1,2-disubstituted cyclopropane in excellent yield and enantioselectivity (84%, *trans:cis* 94:6, *trans* 99% ee). Currently, several oxazolines and Schiff base complexes with rhodium or cobalt salts are used for the enantioselective cyclopropanation reactions.[99]

In 1991, Jacobsen and coworkers[100] reported enantioselective epoxidation reaction of olefins catalyzed by manganese(II)-Schiff base complex **128**. Epoxidation of **127** using sodium hypochloride in the presence of **128** gave **129** in excellent yields and excellent enantioselectivity (up to 96% yields and up to 98% ee). Schiff base-transition metal complexes are also employed along with organometallic reagents in enantioselective reactions. $Cu(OTf)_2$- **131** complex[101]

catalyzed the enantioselective conjugate addition reactions of diethylzinc to cyclic and acyclic enones with high yields and excellent enantioselectivity (77-82%, 78-99% ee). In addition, aluminum-chiral peptide based Schiff base **134** catalyzed[102] 1,2-addition of diethylzinc to pyridyl substituted -ynones **133** gave **135** in good yields and excellent enantioselectivity (<84%, 98% ee).

Scheme 3.24 Selected Transition Metal-Schiff Base or bis-(Oxazolidine) Complex Catalyzed Enantioselective Reactions. [98-102]



The successful implementation of amidine and Schiff bases as organocatalyst for large number of reactions prompted us to investigate the scope of similar nitrogen and phosphorus derivatives for the halofunctionalization reactions. To the best of our knowledge, no examples on Schiff bases catalyzed halofunctionalization reactions were reported in the literature. Hence the main objective of present investigation is to develop new, general and organocatalytic procedures for the regio- and stereoselective halofunctionalization of non-functionalized and functionalized alkenes. In order to perform these halofunctionalization reactions, design and high throughput screening of new organocatalyst is undertaken. Hence, the overarching goals of the project involve:

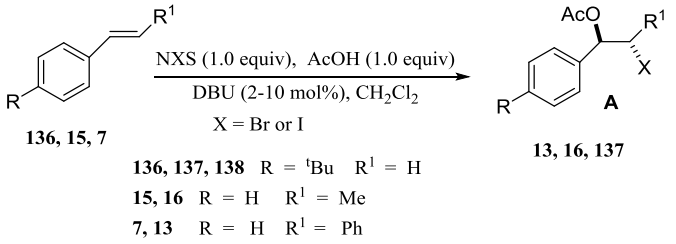
a. Exploring and expanding the scope of *N*-functional groups as organocatalyst for *N*-halonium ion mediated halofunctionalization reaction of alkenes with nucleophiles, including both inter- and intramolecular reactions.
b. Synthesizing and extending the scope of chiral nitrogen and phosphorus compounds for catalytic regio- and stereoselective halofunctionalization reactions.
c. Probe the physical properties and structure of the active catalyst through physical measurements (e.g., NMR, IR, GC/MS and X-ray structure determination of isolated complexes where possible).

3.5 Results

3.51 Vicinal Haloacetoxylation of Cyclic and Acyclic Alkenes

The haloacetoxylation reaction of alkenes catalyzed by amides, amines, and amidines reported in the literature inspired us to investigate the bromoacetoxylation of acyclic alkenes employing DBU as organocatalyst. For this study, 4-*tert*-butyl styrene (**136**) was taken as a test substrate and reacted with NBS (1.0 equiv) and acetic acid (1.0 equiv) in the absence or presence of DBU catalyst (**Table 3.1**, entries 1 and 2 respectively).The controlled experiment confirmed that DBU acted as excellent carrying agent for vicinal *anti*-bromoacetoxylation of **136** affording **137a** in excellent yields and excellent diastereoselectivity (entries 1 vs 2; 23% vs 86%, dr 100:0). Although, the iodoacetoxylation reaction of **136** with NIS also gave corresponding product **138** in excellent yield and excellent diasteroselectivity (entry 3), utilization of NCS under identical condition recovered all starting materials reflecting the less reactive nature of NCS (entry 4). DBU (10 mol %) catalyzed the bromoacetoxylation reaction of trans *β*-methyl styrene in 2 hours (entry 5) and the amount of organocatalyst can be lowered to 2 mol % without diminishing the yield and diastereoselectivity (entries 6-8). The application of 1,3-dibromo-5,5-dimethylhydantoin (DBDH, 1.0 equiv) as brominating agent under identical conditions also retained the yield and diastereoselectivity (entry 7). In all of these reactions, 2-5% of s*yn* haloacetoxylation product was characterized by ^{1}H and ^{13}C NMR spectra of the corresponding products.

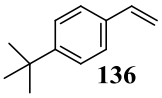
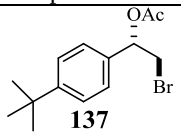
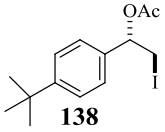
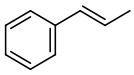
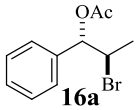
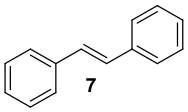
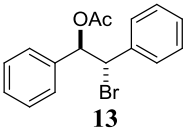
Table 3.1 DBU Catalyzed Bromoacetoxylation Reactions of Acyclic Alkenes.



136, 15, 7

136, 137, 138 R = ^{t}Bu R^1 = H
15, 16 R = H R^1 = Me
7, 13 R = H R^1 = Ph

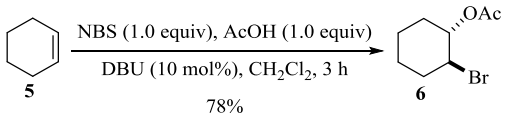
13, 16, 137

entry	substrate	catalyst (mol %)	time (h)	halogen source	product	% yield **A**[a]
1	 **136**	None	12	NBS	 **137**	23
2	**136**	**109** (10)	2	NBS	**137**	86
3	**136**	**109** (10)	2	NIS	 **138**	97
4	**136**	**109** (10)	12	NCS	-[c]	0
5	 **15**	**109** (10)	2	NBS[b]	 **16a**	97
6	**15**	**109** (2)	3	NBS[b]	**16a**	79
7	**15**	**109** (2)	3	DBDMH	**16a**	95
8	 **7**	**109** (2)	4	NBS	 **13**	64

[a] Yields are based upon isolated products purified by flash column chromatography. [b] The major *anti*-diastereomer along with 0-5% of *syn* haloacetoxylation product was also observed in the reaction. Controlled experiment in the absence of catalyst gave ~20-25% product after 12 h. [c] Starting alkene (100%) recovered.

In addition to acyclic alkenes, DBU catalyzed the bromoacetoxylation reaction of cyclic alkene (e.g., cyclohexene, **5**) under previously optimized reaction condition (**Scheme 3.25**).

Scheme 3.25 DBU Catalyzed Bromoacetoxylation Reaction of Cyclohexene.



The participation of DBU as organocatalyst for the haloacetoxylation reaction encouraged us to systemically investigate the effect of large numbers of Lewis base catalysts for the halofunctionalization reaction. Hence, various nitrogen and phosphorus Lewis bases **139-148** were synthesized by the modification of literature procedures and applied them for the halofunctionalization reaction (**Figure 3.1**, see detailed synthetic procedure in experimental sections).

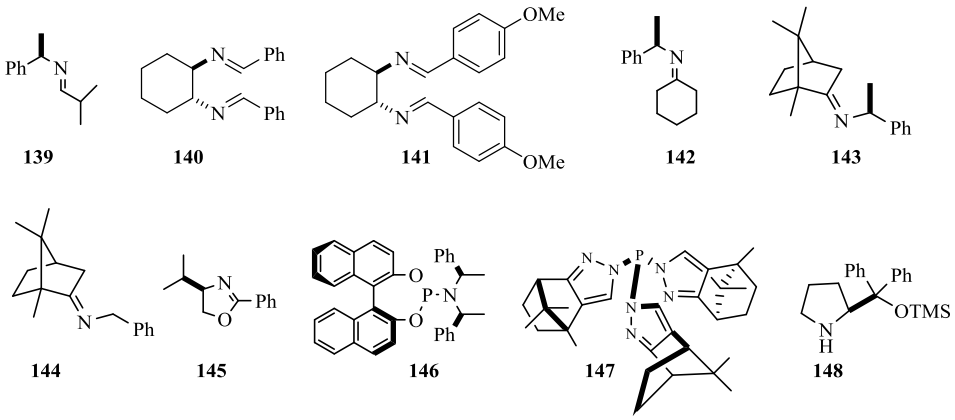
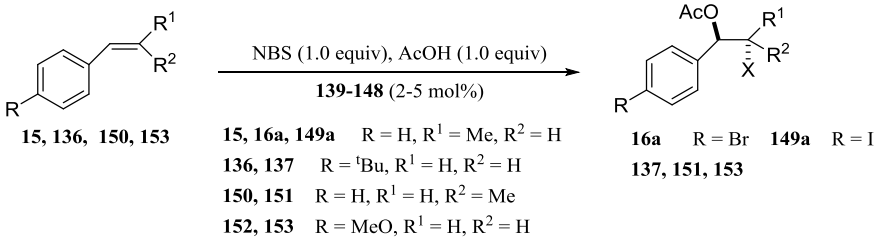


Figure 3.1 Nitrogen and Phosphorus Lewis Bases Screened for Halofunctionalization Reactions.

The results obtained from the utilization of organocatalysts **139-148** for the halofunctionalization reaction were summarized in **Table 3.2**. Under the standard reaction conditions, organocatalysts **139-148** as low as 2 mol% were sufficient for catalyzing the halofunctionalization reactions with excellent yield and diastereoselectivity within a short time

period. In all of the tested reactions, nitrogen bearing Lewis bases such as aldimine **139-141**, ketimines **142-144**, dihydrooxazole **145**, phosphorus compounds **146-147** and diphenylprolinol silyl ether **148** catalyzed the bromoacetoxylation reaction of *trans*-β-methyl styrene **15** affording **16a** in excellent yield and excellent diastereoselectivity (entries 1-12). Although, phosphoramidite **146** catalyzed bromoacetoxylation reaction of **15** gave substantially low yields of product (entry 9), good yields of the iodoacetoxylation product **149a** was observed while using NIS as iodinating agents (entry 10). In addition, phosphorus based chiral tripod ligand **147** also catalyzed the bromoacetoxylation reaction affording corresponding products in excellent yields and diastereoselectivity (entry 10). Next, the olefinic substrates **136**, **150** and **152** which representsthe effect of substrate structure were examined for the bromoacetoxylation reaction. The bromoacetoxylation reaction of *cis-β*-methyl styrene **136** was also catalyzed by aldimine **139-141**, ketimine **142** and **144** affording **151a** as single diastereomeric product in excellent yield (entries 13-18). Aldimine **139** and ketimines **142** also catalyzed the bromoacetoxylation reaction of 4-*tert*-butyl styrene **136** and 4-methoxystyrene **152** affording corresponding products **137** and **153** respectively in excellent yields (entries 19-20).

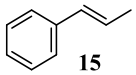
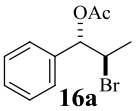
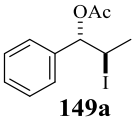
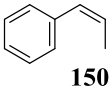
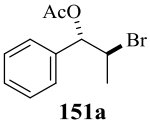
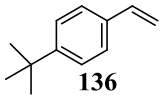
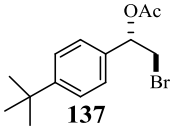
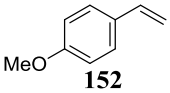
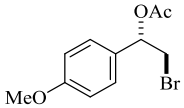
Table 3.2 Catalytic Bromoacetoxylation Reactions of Alkenes **15**, **136**, **149** and **151**.



15, 136, 150, 153

15, 16a, 149a R = H, R^1 = Me, R^2 = H
136, 137 R = ^{t}Bu, R^1 = H, R^2 = H
150, 151 R = H, R^1 = H, R^2 = Me
152, 153 R = MeO, R^1 = H, R^2 = H

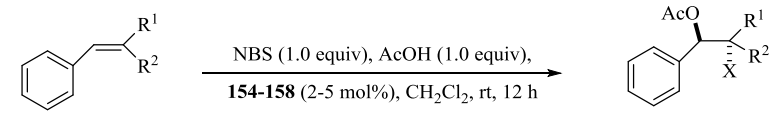
16a R = Br **149a** R = I
137, 151, 153

entry	substrate	catalyst (mol %)	time (h)	halogen source	product	% yield[a]	% ee
1	 **15**	**139** (2)	3	NBS	 **16a**	98	-
2	**15**	**140** (2)	3	NBS	**16a**	82	-
3	**15**	**141** (2)	3	NBS	**16a**	79	-
4	**15**	**142** (2)	2	NBS	**16a**	95	
5	**15**	**143** (2)	6	NBS	**16a**	88	0
6	**15**	**143** (2)	4	DBDMH[b]	**16a**	94	-
7	**15**	**144** (2)	4	NBS	**16a**	84	0
8	**15**	**145** (5)	4	NBS	**16a**	95	0
9	**15**	**146** (2)	12	NBS	**16a**	25	0
10	**15**	**146** (2)	4	NIS	 **149a**	75	0
11	**15**	**147** (2)	4	NBS	**16a**	92	6.5
12	**15**	**148** (2)	4	NBS	**16a**	89	0
13	 **150**	**139** (2)	12	NBS[c]	 **151a**	89	0
14	**150**	**140** (2)	3	NBS	**151a**	86	6
15	**150**	**141** (2)	3	NBS	**151a**	73	15[d]
16	**150**	**142** (2)	6	NBS	**151a**	85	0
17	**150**	**144** (10)	4	NBS	**151a**	85	10
18	 **136**	**139** (2)	3	NBS	 **137**	95	-
19	**136**	**142** (2)	3	NBS	**137**	89	-
20	 **152**	**139** (2)	4	NBS	 **153**	93	-

[a] Yields are based on isolated products after flash column chromatography. 0-5% of syn isomer was characterized by ^{1}H and ^{13C} NMR. [b] Reaction ran at -40 ^{o}C. [c] Reaction ran at 0 ^{o}C. [d] 23% ee was observed while using chiral schift reagents; erbium tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorate.

We also synthesized chiral imidazolium salts **154-158** using slight modification of the literature procedures[103-105] and used them for the halofunctionalization reactions. These reactions gave halofunctionalization product with moderate to good yield but excellent diastereoselectivity.

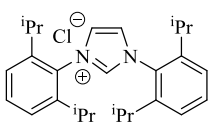
Table 3.3 Imidazolium Salt Catalyzed Bromoacetoxylation Reaction.



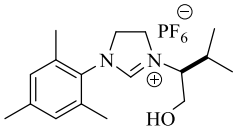
15, 151 **16a, 152**

15, 16a R^1 = Me, R^2 = H

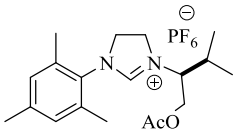
151, 152 R = H, R^1 = H, R^2 = Me



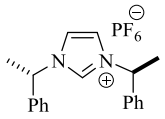
154



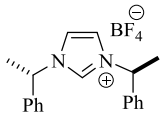
155



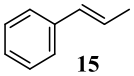
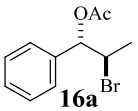
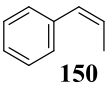
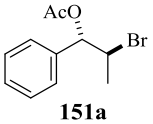
156



157



158

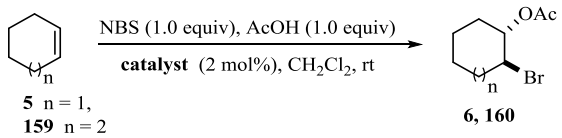
entry	substrate	catalyst	product	isolated yield[a]	% ee
1	 **15**	**154**	 **16a**	87	-
2	**15**	**155**	**16a**	23	-
3	**15**	**156**	**16a**	39	-
4	**15**	**157**	**16a**	84	-
5	**15**	**158**	**16a**	82	-
6	 **150**	**154**	 **151a**	75	-
7	**150**	**155**	**151a**	43	0
8	**150**	**156**	**151a**	54	5
9	**150**	**157**	**151a**	64	6
10	**150**	**158**	**151a**	86	5

[a] Yields are based on isolated products after flash column chromatography. 0-5% of syn-isomer was characterized by ^{1}H and ^{13}C NMR spectrum.

Although our initial objective was to develop new methodology for the enantioselective bromo/iodoacetoxylation reaction of olefins employing chiral nitrogen and phosphorus catalyst **139-148** and **155-158**, we failed to aechieve enantioselectivity in most of the reaction. The bromoacetoxylation reactions of *cis-β*-methyl styrene **150** catalyzed by imine **140, 141** and **144** gave **151a** in good yields and excellent diastereoselectivity, enantintioselectivty was quite poor (15 %ee was observed with chiral HPLC while 23% ee was observed when chiral schift reagents; erbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate was used]; **Table 3.2**; entry 15). The lower enantioselectivity in the bromoacetoxylation reactions was expected due to the non-rigid nature of chiral organocatalyst which failed to lock the transition state conformations of the bromonium ion intermediate and hence gave the racemic product.

Not surprisingly, bromoacetoxylation reaction of cyclic alkenes **5** and **159** were efficiently catalyzed by imines **139**, **142** and **143** with excellent yields and excellent diastereoselectivity but again with no enantioselectivity.

Table 3.4 Bromoacetoxylation Reaction of Cyclic Alkenes.



5 n = 1,
159 n = 2

6, 160

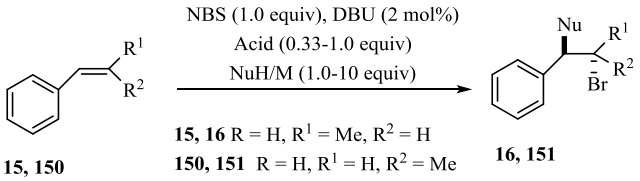
entry	substrate	catalyst	time (h)	% yield **6** or **160**[a]	% ee
1	**5**[b]	**139**	3	95	0
2	**5**	**142**	2	79	3
3	**5**	**143**	6	78	0
4	**159**	**142**	2	86	0
5	**159**	**143**	6	88	0

[a] Yields are based on isolated pure compounds obtained after flash column chromatography. [b] Reaction in the absence of catalyst gave ~10% yield after 12 h.

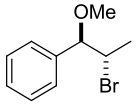
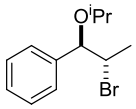
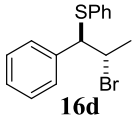
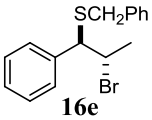
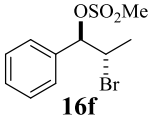
3.52 Nucleophilic Scope in Halofunctionalization Reactions

These encouraging results on haloacetoxylation reaction of alkenes employing nitrogen and phosphorus catalysts **139-148** lead us to examine the nucleophilic scope in the halofunctionalization reaction. Although DBU (2 mol %) failed to catalyze the bromoetherification reaction of *trans-β*-methyl styrene **15** in the presence of excess amounts of methanol (**Table 3.5**, entry 1), the bromoetherification product **16b** was observed in excellent yield while using acetic acid (1.0 equiv) along with excess amounts of methanol (10.0 equiv, entry 2). The minor amount of bromoacetoxylation by-product **16a** was also observed in the reaction due to competing side reaction. The use of catalytic amounts of acetic acid (10 mol %) also promoted the bromoetherification reaction but with much lower yield (60%, entry 3). In this reaction, 40% starting material was also recovered. The formation of bromoacetoxylation by-product lead us to modify the procedure employing non-nucleophilic citric acid rather than nucleophilic acetic acid as a source of H^+ ion in the haloetherification reaction. The DBU catalyze bromoetherification reaction of *trans-β*-methyl styrene **15** underwent efficiently while employing citric acid (0.5 equiv or 0.33 equiv) in excellent yield, regio- and diastereoselectivity (entries 4, 5 respectively). An application of isopropyl alcohol in the bromoetherification reaction also gave similar yields (entry 6). In a subsequent experiment, we decided to examine the vicinal etherification reaction of *trans-β*-methyl styrene **15** using phenol and thiophenol as nucleophile in the presence of citric acids. However, in both of these reactions all starting material was recovered (entries 7, 8). A modification of the procedure using stoichiometric in acetic acid and excess amounts of thiophenol (10.0 equiv) or benzyl thiol (10.0 equiv) however gave a moderate yield of bromothioether **16d** and **16e** respectively (entries 9 and 10).

Table 3.5 Vicinal Bromofunctionalization Reactions of *trans*-*β*-Methylstyrene



a Nu = OAc **b** Nu = OMe **c** Nu = ^{i}Pr
d Nu = PhS **e** Nu = $PhCH_2S$ **f** Nu = $MeSO_2O$

entry	substrate	acid (equiv)	NuH/M (equiv)	product[a]	% yield[b]
1	**15**	-	MeOH (10)	-	trace[c]
2	**15**	AcOH (1.0)	MeOH (10)	 **16b**	75[d]
3	**15**	AcOH (0.1)	MeOH (10)	**16b**	60[e]
4	**15**	citric acid (0.5)	MeOH (10)	**16b**	89
5	**15**	citric acid (0.33)	MeOH (10)	**16b**	90
6	**15**	citric acid (0.33)	^{i}PrOH (10)	 **16c**	85
7	**15**	citric acid (0.33)	PhOH (4)	SM	-
8	**15**	citric acid (0.33)	PhSH (4)	SM	-
9	**15**	AcOH (1.0)	PhSH (10)	 **16d**	56
10	**15**	AcOH (1.0)	$PhCH_2SH$ (10)	 **16e**	58
11	**15**	-	$MeSO_3H$ (1.1)	 **16f**	90

[a] Major *anti* halofunctionalized product was reported. 0-5% minor *syn* isomer was also observed in the reaction. [b] Yields are based upon isolated product after flash column chromatography. [c] Trace amounts of product was characterized by ^{1}H NMR and GC/MS of the crude product. [d] Bromoacetoxylation product (25%) was observed as a by-product of the reaction. [e] Starting materials (40%) was isolated.

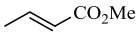
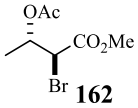
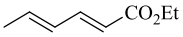
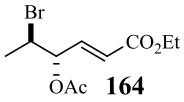
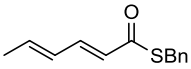
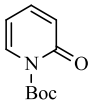
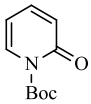
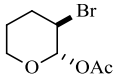
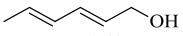
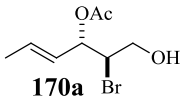
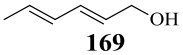
Methane sulfonic acid also acted as a nucleophilic Brønsted acid in the vicinal bromosulfonylation reaction affording **16f** in excellent yields and diastereoselectivity (entry 11). Attempted insitu generation of CN^-, SCN^-, NO_2^- and N_3^- nucleophiles and their use for the bromofunctionalization reaction of *trans-β*-methyl styrene failed to give the desired products [nitrous acid (HNO_2), hydrogen azide (HN_3), hydrogen cyanide (HCN) and hydrogen thiocyanide (HSCN) were synthesized in situ from the reaction of Na or K salts of CN^-, SCN^-, NO_2^- or N_3^- with TMSCl (1.0 equiv) and water (0.5 equiv) and reacted with *trans-β*-methyl styrene in the presence of DBU catalyst]. In these experiments, *anti* 1-chloro-1-phenyl-2-bromo propane was observed exclusively.[106] All the examples investigated above confirmed the versatility of our catalyst for the halofunctionalization reaction of alkenes.

3.53 Halofunctionalization Reaction of Electron Deficient and Electron Rich Alkenes

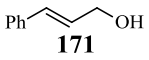
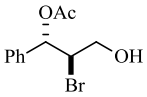
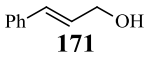
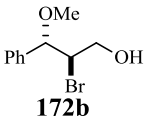
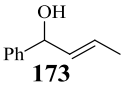
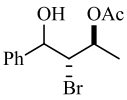
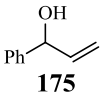
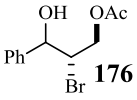
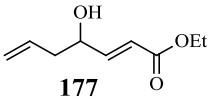
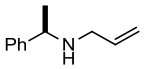
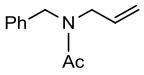
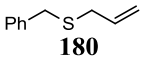
After optimizing the conditions for the halofunctionalization reaction of acyclic and cyclic nonfunctionalized alkenes, we were keen to adopt the methodology for the halofunctionalization reaction of electron deficient and electron rich alkenes. Our initial attempt for the DBU catalyzed bromoacetoxylation reaction of methyl crotonate **159** with stoichiometric amounts of NBS and acetic acid failed (**Table 3.6**, entry 1). However, the modification of procedure using trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.0 equiv) to the reaction mixture in the absence of DBU under otherwise identical reaction conditions gave moderate yields of bromoacetoxylation product **163** (entry 2). The regioselective bromoacetoxylation reaction of the *γ,δ*-double bond of ethyl sorbate **164** also promoted efficiently in the presence of TMSOTf (1.0 equiv, entry 3). Despite these successful examples, attempted bromoacetoxylation reaction of 2,4-hexadiene thiolate **165** in the presence of TMSOTf (1.0 equiv) cleaved the thioester moiety (entry

4) while attempted bromoacetoxylation reaction *N*-Boc-2-pyridone (**166**) in the presence or absence of TMSOTf failed under identical reaction condition (entries 5-6).

Table 3.6 Bromofunctionalization Reactions of Electron Deficient and Electron Rich Alkenes.

entry	substrate	DBU mol %	NuH	time (h)	Product	% yield [a]
1	 **161**	2	AcOH	24	SM	-
2	**161**	-[b]	AcOH	12	 **162**	67
3	 **163**	-[b]	AcOH	12	 **164**	79
4	 **165**	-[b]	AcOH	24	-[c]	-
5	 **166**	2	AcOH	12	SM	-
6	 **166**	-[b]	AcOH	12	SM	-
7	 **167**	2	AcOH	12	 **168**	75
8	 **169**	2	AcOH	4	 **170a**	85
9	 **169**	-	-	4	-	-

[a] Yields are based upon isolated products obtained after flash column chromatography. [b] The reaction was carried out in the presence of TMSOTf (1.0 equiv). [c] Thioester was cleaved during the reaction.

entry	substrate	DBU mol %	NuH	time (h)	Product	% yield [a]
10	 **171**	2	AcOH	4	 **172a**	82
11	 **171**	2	MeOH[b]	4	 **172b**	80
12	 **173**	2	AcOH	3	 **174**	87
13	 **175**	2	AcOH	4	 **176**	76
14	 **177**	2	AcOH	12	-	-
15	 **178**	2	AcOH	12	-	-
16	 **179**	2	AcOH	12	-	-
17	 **180**	2	AcOH	12	-	-

[a] Yields are based upon isolated products after flash column chromatography. [b] Citric acid (0.33 equiv) was used.

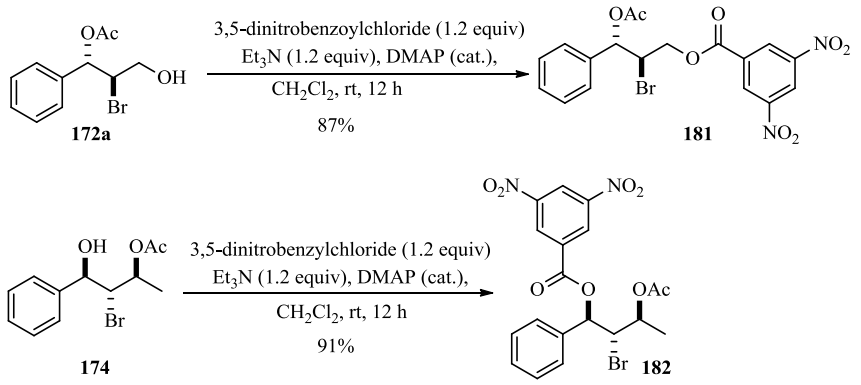
Not surprisingly, our catalytic systems exhibited their high efficiency for the regio- and diastereoselective halofunctionalization reactions of electron rich double bond. The application of the procedure catalytic in DBU (2 mol%) in the reaction of 2H-pyran (**167**) with NBS (1.0 equiv) and AcOH (1.0 equiv) afforded **168** in good yield (entry 7). Besides, DBU catalyzed bromoacetoxylation reaction of electron rich double bond of 1,3-hexanediol **169** gave excellent yields of **170a** (entry 8). The controlled experiment in the absence of DBU recovered all starting materials (entry 9). DBU catalyzed bromoacetoxylation reactions of cinnamoyl alcohol (**171**), 1-

phenyl-2-buten-1-ol (**173**) and 1-phenyl-2-propen-1-ol (**175**) also underwent efficiently affording corresponding products **172a**, **174** and **176** respectively in excellent yields and diastereoselectivity (entries 10, 12, 13). In addition, bromoetherification reaction of cinnamoyl alcohol (**171**) gave **172b** in excellent yield and diastereoselectivity. The halofunctionalization reaction of allyl alcohols **173** and **175** provided opportunity for the generation of three contiguous chiral centers in acyclic vinyl alcoholic substrate in a single reaction step with high regio- and diastereoselection. The application of identical reaction conditions for the haloacetoxylation reaction of hydroxyenoate **177** (entry 14), allylic amines **178-179** (entries 15, 16) and allylic thioether **180** (entry 17) failed. In a mean time when we were investigating the halofunctionalization reaction of electron rich and electron deficient olefins, two groups reported their independent findings in the enantioselective halofunctionalization reactions. In 2011, Nicolaou and coworkers[107] reported the dimeric cinchona alkaloid [$(DHQD)_2PHAL$ or peudoenantiomer] catalyzed enantioselective dichlorination reaction of allyl alcohol using iododichlorides as the source of chlorenium ions and chlorine anions on high yields and high enantioselectivity (upto 90% yields and 85% ee). These reactions could be used for the synthesis of oligo- and polychlorinated compounds present in several natural products.[108] Two years laters, Tang and coworkers[109] reported the bromofuntionalization reaction of cinnamoyl alcohol and allylic amines using $(DHQD)_2PHAL$ as organocatalyst (42-82% yields, 17-40% ee for cinnamoyl alcohol and 20-82% yields, 21-90% ee for allylic amines).

The stereochemistry of the bromoacetoxylation products **172a** and **174** observed in the above reactions were determined by synthesizing corresponding 3,5-dintrobenzoyl derivatives **181** and **182** followed by their single crystal X-ray crystallography (**Scheme 3.26**). 50% Probability thermal ellipsoids for **181** is reported in **Figure 3.4**. Crystal data and structural

refinement are reported in **Table 3.9**. Crystallographic information (CIF) file is reported in appendix A.

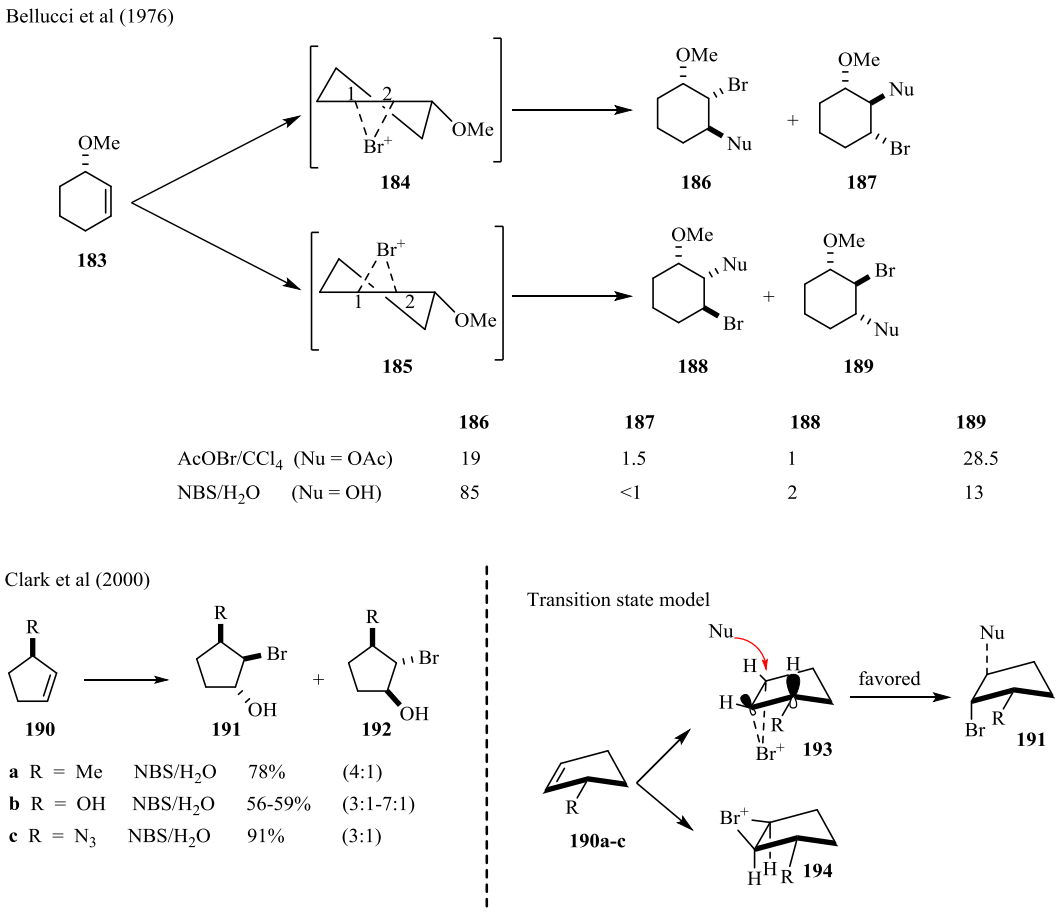
Scheme 3.26 3,5-Dinitrobenzoyl Derivatives of Bromoacetoxylation Products.



In a subsequent study, we were interested to investigate the halofunctionalization reaction of cyclic allyl alcohol using the procedure catalytic in DBU. Existing halogenation protocols mostly gave low regio- and stereoselectivity for the cyclic allylic system.[110-112] Bellucci and coworkers[112] reported the bromofunctionalization reaction of 1-methoxy-2-cyclohexene **183** using AcOBr/CCl_4 or NBS as brominating agents; however, these reactions gave the mixture of different regio- and diastereomeric products (i.e., **186**, **187**, **188** and **189**, **Scheme 3.27**). The authors claimed that the stereoselectivity in the bromofunctionalization reaction occurred at the electrophilic addition step while the regioselectivity of the products was controlled during the nucleophile addition. The electrophilic addition of bromonium ion to **183** gave two transition states **184** and **185**. The *syn:anti* addition of bromonium ion from AcOBr to the C=C bond of 4-methoxy cyclohexene was expected in 4:6 ratio while the nucleophilic attack of AcO^- at C1 or C2 of cis and trans bromonium ions was expected in the ratio of 9:1. Hence, the stereoselectivity reported reflects **186**+**187**:**188**+**189** ratio and regioselectivity includes **186**:**187** and **188**:**189**. Besides, authors also claimed that the regioselectivity of the nucleophilic step was independent to

the reaction conditions but depends upon the electronegative substituent (i.e., OMe). The reaction of NBS/H_2O system with 2-methoxycyclohexene **183** however had high preferences for the *syn*-electrophilic attack and that lead to different stereo- and regioselectivity probably due to the differences in the steric courses of brominating reagents. Clark and coworker's[113] similar investigation on cyclopentyl allylic system gave poor regioselectivity despites affording good yield of products. The authors claimed that NBS/H_2O addition to **190a-c** gives the *syn*-bromonium ion intermediate with respect to the allylic substituent. It was believed that allyl substituted cyclopentenes **190a-c** exist in envelop conformation with equatorial R substituent. The *syn*-addition of Br^+ ion to the substrate gives transition state **193** and **194**. The transition state **193** can be stabilized by anomeric effect where axial allylic C-H σ-bond acts as electron releasing group and stabilizes the bromonium ion by back donation into the C-Br σ*-bond. Besides, the *syn*-bromonium ion TS **193** was expected to have lower energy than that of *anti*-bromonium ion TS **194** due to steric reason hence the major product can be formed from transition state **193**.

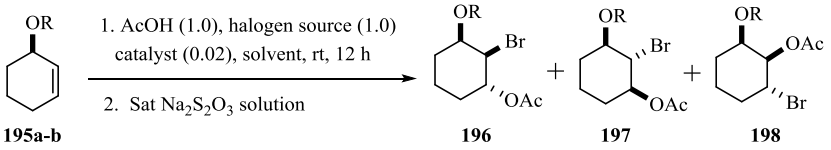
Scheme 3.27 Transition state Models for the Halofunctionalization of Cyclic Allyl Alcohols. [112,113]



We also investigated the halofunctionalization reaction of cyclic vinyl alcohol **195a** and **195b** using a procedure catalytic in DBU. The bromoacetoxylation reaction of **195a** with NBS (1.0 equiv) and AcOH (1.0 equiv) gave good yield of products at room temperature but with poor regio- and diastereoselectivity (**Table 3.7** entry 1). In this reaction, three major regio- and diastereomeric products were observed along with minor amounts of unidentified mixture. Running the reaction at lower temperature (entry 2) or the use of catalytic amounts of ketimine **144** under identical reaction conditions did not improve the yield, regio- and diastereoselectivity (entry 3). Although, the reaction in coordinating solvent (e.g., THF in entry 4) gave complex

mixtures, the use of acetonitrile gave better regio- and diastereoselectivity (entry 5). The use of more reactive brominating agents (i.e., DBDMH in entries 6 and 7) also did not improve the yield, regio- and diastereoselectivity. Attempted DBU catalyzed bromoacetoxylation reaction of *tert*-butyldimethylsilyl protected 2-cyclohexenol (**195b**) also afforded a complex mixture of several unidentified products. The regioisomeric products **196-198** observed in the reaction were characterized by comparing their NMR spectra with the products obtained in the halofunctionalization reaction of 2-cyclopentenol (**Scheme 3.27**)[113] however actual identification of regioisomeric product **196-198** needed the syntheses of corresponding 3,5-dinitrobenzoyl derivatives and their single crystal X-ray analysis in future.

Table 3.7 Bromoacetoxylation Reactions of Cyclic Allyl alcohol.



195a-b **196** **197** **198**

a R = H

b R = ^{t}BuMe$_2$Si

entry	substrate	halogen source	solvent	catalyst (mol%)	ratio (**196: 197:198**)[a,b]	% conversion[b]
1	**195a**	NBS	CH_2Cl_2	**109** (2)	3:2:0	63
2	**195a**	NBS	CH_2Cl_2	**109** (2)[c]	1.05:1.03:1.0	69
3	**195a**	NBS	CH_2Cl_2	**144** (2)	5:3:2.5:1:0	66
4	**195a**	NBS	THF	**109** (2)	-	trace
5	**195a**	NBS	CH_3CN	**109** (2)	8.2:3.2:1.0	67
6	**195a**	DBDMH	CH_2Cl_2	**109** (2)	1.37:1.33:1.0	66
7	**195a**	DBDMH	CH_2Cl_2	**109** (2)[c]	1.0:1.5:1.4	69
8	**195b**	NBS	CH_2Cl_2	**109** (2)	-	trace

[a] The ratio of three different products was determined by measuring ^{13}C-NMR peaks height of carbinol carbon of corresponding products. [b] Ratio of different products and % conversion was calculated from the GC ratio of crude products . [c] Reaction ran at 0 ^{o}C.

3.54 Halocyclization Reactions

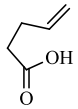
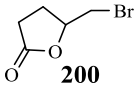
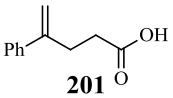
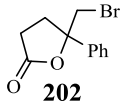
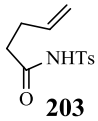
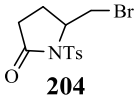
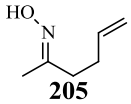
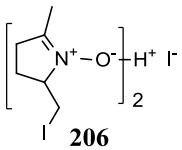
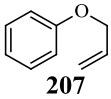
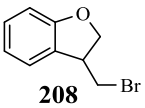
Halogen promoted cyclization of unsaturated acids and unsaturated amides are commonly used methods for the construction of halogenated heterocyclic ring present in several natural products in organic chemistry. Among them, the chemistry of halolactonization reaction has been increasingly investigated in the last decades. Much of the efforts in the recent years are focus on controlling the enantioselectivity of the newly generated chiral centers employing organocatalytic or transition metal catalysts (vide supra). We successfully employed our organocatalytic system for the halocyclization reactions of unsaturated acids, unsaturated amides and unsaturated ethers.

A controlled experiment involving the reaction of 4-pentenoic acid with NBS (1.0 equiv) in the absence of organocatalyst gave a minor amounts of bromolactone **156** (12%) at room temperature after 12 hours (**Table 3.8**, entry 1). However, when the reaction was carried out in the presence of catalytic amounts of DBU (2 mol %) or chiral imine **146** (5 mol%) under identical reaction conditions, bromolactone **200** was observed in excellent yields (entries 2 and 3 respectively). The catalytic amounts of DBU also promoted the bromolactonization reaction of 4-phenyl-4-pentenoic acid **201** affording bromolactone **202** in excellent yield (entry 4). Besides, a bromocyclization reaction of *N*-tosyl-4-pentene **203** was also catalyzed by DBU affording bromolactam **201** in good yields (entry 5).

Unsaturated ketoxime **205** underwent iodocyclization reaction with molecular iodine even in the absence of DBU affording iodoiminol salt **206** in excellent yields (entry 6). Surprisingly, bromocyclization reaction of phenyl vinyl ether **207** with NBS was also catalyzed by DBU affording (bromomethyl)dihydrobenzofuran **208** in moderate yields (entry 7). The newly developed methodology for the bromocyclization reaction of **207** in our laboratory overcame the limitation of literature method for the syntheses of **208** using arenediazonium tetrafluoroborates

with copper (II) chloride/bromide in dimethyl sulfoxide, which was proceeded via highly reactive radical ion pathway.[114] All of the tested protocols confirmed the versatility of our catalytic system for intramolecular halofunctionalization reactions.

Table 3.8 Halocyclization Reaction of Unsaturated Acids, Amide and Ether.

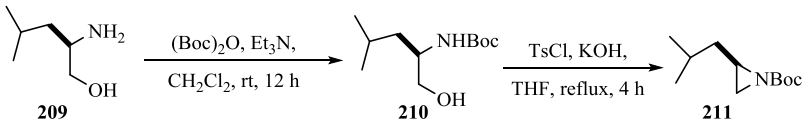
entry	substrate	catalyst (mol %)	halogen source	time (h)[a]	product	% yield[b]
1	 **199**	-	NBS	12	 **200**	12
2	**199**	**109** (2)	NBS	1	**200**	95
3	**199**	**145** (5)	NBS	3	**200**	90
4	 **201**	**109** (2)	NBS	2	 **202**	82
5	 **203**	**109** (2)	NBS	6	 **204**	74
6	 **205**	-	I_2	12	 **206**	85
7	 **207**	**109** (2)[c,d]	NBS	12	 **208**	78

[a] All reactions were run in the room temperature and quenched at that temperature after stirring for indicated time. [b] Yields are based upon the isolated products purified by flash column chromatography. [c] Starting material (~ 5%) was also recovered along with desired product. [d] Citric acid (0.33 equiv) was used.

3.55 Synthesis of Chiral Bicyclic Catalyst

The non-rigid chiral acyclic imines **139-144** (**Figure 3.1**) used for inter- and intramolecular halofunctionalization reactions gave racemic products. Hence the necessity of more rigid chiral bicyclic imines was realized during our investigation. In order to synthesize chiral bicyclic imine, a route involving *α*-alkylation of *N*,*N*-dimethylcyclohexanyl hydrazone with chiral aziridinyl derivatives followed by in situ cyclization of the intermediate to form the final product was designed. For this purpose, *N*-Boc protected aziridine was synthesized from L-leucinol by using the procedure reported in the literature.[115] L-Leucinol **209** was readily converted into *N*-Boc protected alcohol **210** using a standard procedure, which was then transformed into aziridine **211** upon the treatment of a base (20% KOH, **Scheme 3.28**).

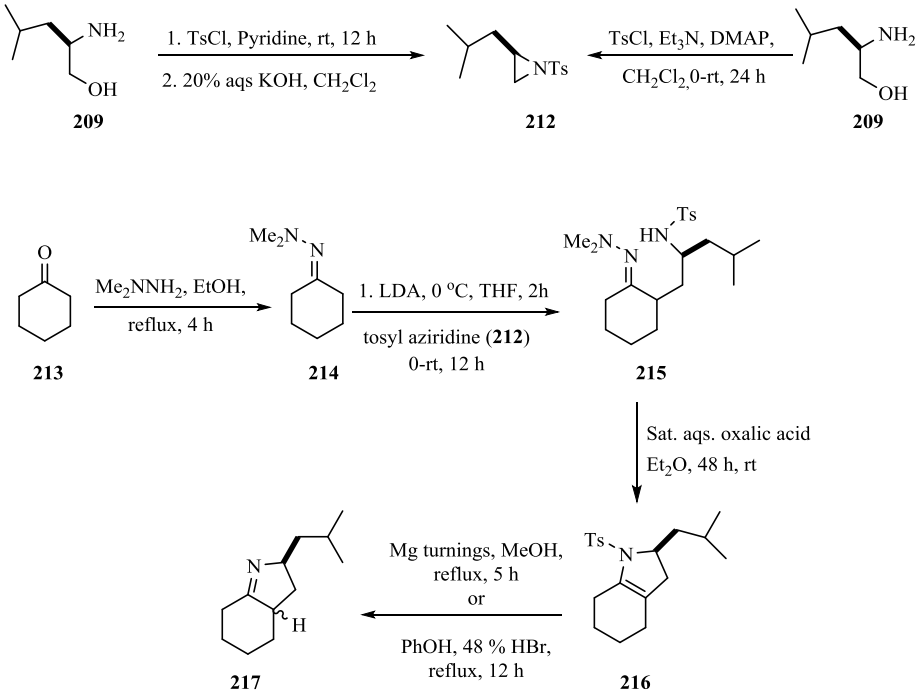
Scheme 3.28 Syntheses of *N*-Boc Protected Chiral Aziridine.[115]



Although several examples of aziridine ring opening using lithium enolates were reported in the literature, attempted opening of *N*-Boc protected aziridine **211** using lithium enolate derived from cyclohexanone or *N*,*N*-dimethylcyclohexanyl hydrazone enolate failed in our laboratory. The low reactivity of *N*-Boc protected aziridine **211** with cyclohexanyl lithium enolate or *N*,*N*-dimethylcyclohexanyl hydrazone enolate was rationalized due to poor electron withdrawing nature of *N*-Boc group. In order to enhance the reactivity of aziridinyl substrate, a more electron withdrawing group in the nitrogen atom of the aziridine ring was realized hence the syntheses of chiral *N*-tosyl aziridine was carried out using a literature procedure.[116] The reaction of L-leucinol **209** with *p*-toluenesulfonyl chloride (TsCl, 2.2 equiv) in pyridine gave *bis*-tosyl-

protected intermediate which on treatment with potassium hydroxide in pyridine afforded the aziridinyl tosylate **212**. The purity and dryness of both pyridine and TsCl was highly essential for the success of this reaction (usually TsCl was recrystallized and pyridine was freshly distilled before using for the reaction). Alternatively, aziridinyl tosylate **212** was synthesized during the reaction of L-leucinol **209** with TsCl (2.2 equiv), Et_3N (4.4 equiv) in the presence of catalytic amounts of *N*,*N*-dimethylaminopyridine (DMAP) in dichloromethane.[117] The reaction of lithium enolate of *N*,*N*-dimethyl-cyclohexanyl hydrazone **214** with aziridinyl tosylate **212** gave the aziridine ring opening product **215**. The cleavage of *N*-tosyl group on treating with saturated aqueous oxalic acid solution in Et_2O followed by attempted deprotection of tosyl group in **216** on refluxing the reaction mixture with Mg turnings in MeOH for 5 hours gave bicyclic imine **217** in good yields but with poor diastereoselectivity (3:1 dr). [118] On the other hand, refluxing **216** with PhOH (2.0 equiv) and 48 % HBr (5.0 equiv)[119] gave good yields of bicyclic imine **217** but again with poor diastereoselectivity (3:1 dr). Attempted separation of both diastereomers of bicyclic imines using flash column chromatography using neutral silica failed and hence further attempt on the syntheses of bicyclic imines was abandoned.

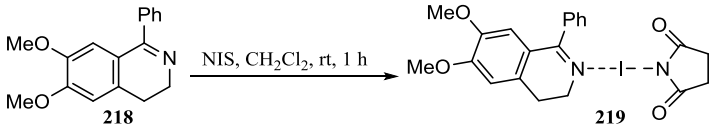
Scheme 3.29 Syntheses of Chiral Bicyclic Imine.



3.56 Solution and Solid State Structural Studies

In order to understand the mechanism of DBU catalyzed halofunctionalization reaction of acyclic and cyclic alkenes, controlled experiments involving solution and solid state structural study of DBU-NBS (1:1 ratio) complex was realized. Previously, Castellote and coworkers[120] successfully isolated a complex during the reaction of imine **218** with NIS (1:1 ratio) and characterized by X-ray crystallography. The single crystal X-ray crystallography of **219** showed that the nitrogen atom of the imine was linearly bonded to the iodine atom of NIS via halogen bonding[121] and gave a planar structure.

Scheme 3.30 Imine-NIS Complex.



Our study also suggested that the strength of the N-X bond played a major role in the success of halofunctionalization reactions as NCS failed to promote the chlorofunctionalization reaction under the reaction condition where bromo/iodofunctionalization reactions were promoted. In order to understand the solution state structure for the bromoacetoxylation reactions of alkenes, a series of NMR experiments were carried out. In this study, ^{13}C NMR of pure DBU, NBS and AcOH was taken separately and their NMR data were compared to the corresponding peaks in the mixture in different ratios. The overlapping of proton peaks of these compounds in the reaction mixture gave complex spectrum and denied us to use ^{1}H NMR data for the characterization of complexes. ^{13}C NMR of pure DBU in $CDCl_3$ showed peaks at 23.3, 25.8, 28.4, 29.6, 37.2, 40.1, 48.3, 52.7 and 161.0 ppm while NBS showed peaks at 28.7 (CH_2) and 173.1 (C=O) ppm and AcOH showed at 20.8 (CH_3) and 177.9 (C=O) ppm in $CDCl_3$. The mixture of DBU and NBS (1:1 ratio) showed peaks at 20.8, 24.2, 27.1, 28.7, 29.8, 33.3 (br), 42.5 (br), 48.1, 53.1, 163.3 (multiplet) and 183.4 (multiplet) ppm. The observation of multiple peaks at 163.3 and 183.4 ppm suggested the equilibration of several closely lying complex structures in the mixture. After 15 minutes, the mixture turned into brownish solution which showed two set of peaks: at 19.0, 23.5, 26.3, 28.5, 29.4 (br), 31.9, 37.5, 48.4, 54.1 and 165.6 ppm for major components and peaks at 16.5, 22.7, 28.2, 29.3, 36.6, 45.0, 50.8, 176.0, and 178.7 (br) ppm for minor components. The overlapping of some of the ^{13}C peaks showed less number of carbon peaks which complicated their identification. The mixture of DBU and AcOH (1:1 ratio) showed a new set of peaks at 19.4, 23.5, 23.8, 26.7, 28.8, 31.7, 37.7, 48.3, 53.9, 165.7, and 176.7 ppm.

The addition of NBS (1.0 equiv) to the resulting mixture showed ^{13}C NMR peaks at 19.3, 22.9, 23.7, 26.6, 28.7, 28.8, 32.0, 37.8, 48.4, 52.0, 165.8, 175.6 and 176.4 ppm. Similar NMR spectra was observed during the addition of AcOH (1.0 equiv) to the mixture of NBS and DBU (1:1 ratio). The complete decomposition of NBS into succinimide and bromonium ion intermediate was not found as ^{13}C NMR peaks corresponding to succinimide (29.5 for CH_3 and 177.8 for C=O) were not observed in the NMR. Although, these results were interpreted as evidence for the formation of a complex during the reaction, attempted crystallization of the saturated brownish solution of DBU-NBS mixtures failed to deliver crystals. Besides, attempted crystallization of the stoichiometric mixture of DBU with NIS or aldimine and ketimines **139-144** with NBS /NIS also failed. The lack of crystal in these experiments denied us to identify the reacting species formed in the halofunctionalization reactions.

3.6 Discussion

The halofunctionalization of alkenes with *N*-halonium ion sources in the presence of nucleophile usually proceed via halonium ion intermediates. The feasibility of such processes however dependent upon several factors including the strength of N-X bonds (e.g., N-F, N-Cl, N-Br or N-I), types of substrate (e.g., cyclic or acyclic, electron rich or electron deficient alkenes), types of reactions (e.g., intermolecular or intramolecular), catalyst employed (Lewis acids, Lewis base, Brønsted acids or phase transfer catalysts)[4] and nature of solvents (e.g., coordinating solvent: THF, Et_2O, EtOAc or non-coordinating solvent: dichloromethane, toluene). The character of the $N\text{-}X^+$ interaction also affects complex formation, dynamic exchanges, rate of reaction, and stereoselectivity. For example, reativity of ICl > I_2 by a factor of 400 in iodolactonization reaction,[122] iodolactionization is faster than bromolactonization,[59, 123] exchange of I^+ between two

different amines is rapid at -78 °C,[59] halogen electron acceptor ability is I > Br > Cl,[121] and N-X bond strength increases with gas-phase basicity of the amine.[121] For $(amine)_2I^+$ complexes, the rate of disassociation to the monomer (i.e., $(amine)X^+$) complex is 250 times slower than the $(amine)_2Br^+$ complex, but the partition ratio between reaction with substrate and reformation of the dimer is three times greater.[13] This was also supported by our haloacetoxylation reactions of acyclic and cyclic alkenes with *N*-halosuccinimide and *N*-halohydantoin. DBU catalyzed chloroacetoxylation reaction of *trans*-β-methyl styrene **15** with NCS and AcOH failed under the condition where NBS, DBDMS or NIS gave excellent yield of corresponding products. In these reactions, DBU acted as a Lewis base catalyst for the transfer of halonium ion from NXS to alkene C=C bond and formed halonium ion intermediate. The S_N2 opening of the halonium ion by nucleophile gives the *anti* vicinal halofunctionalized product. The *N*- and *P*-centered catalysts developed and examined for halofunctionalization reactions in our laboratory enormously expanded the field of Lewis base catalysis. These observations provide powerful opportunities to extend electrophilic halofunctionalization reactions on alkene beyond epoxidation, dihydroxylation, and hydroboration. Not surprisingly, Schiff bases **139-144** applied for the bromo/iodo acetoxylation reaction gave corresponding products in high yields and high *anti* diastereoselectivity.

The formation of *anti*-haloacetoxylation product suggested the participation of halonium ion intermediate in the reaction. A possible mechanism for the reaction involved the formation of DBU-NBS complex **220** during the reaction of DBU with NBS (**Figure 3.2**). This complex **220** may transfer Br^+ to *trans β*-methyl stryrene in the presence of acid to give the intermediate **221.** The regioselective S_N2 opening of bromonium ion intermediate **221** at electron deficient carbon by acetate ion give the final product **16a**. The formation of intermediate structure **222** through the protonation of DBU followed by their hydrogen bonding with carbonyl group in the succimide

was ignored as the NMR experiment invoving the reaction of DBU with NBS and AcOH (1.0 equiv each) did not show the peaks corresponding to carbonyl and methylene carbon of succinimide

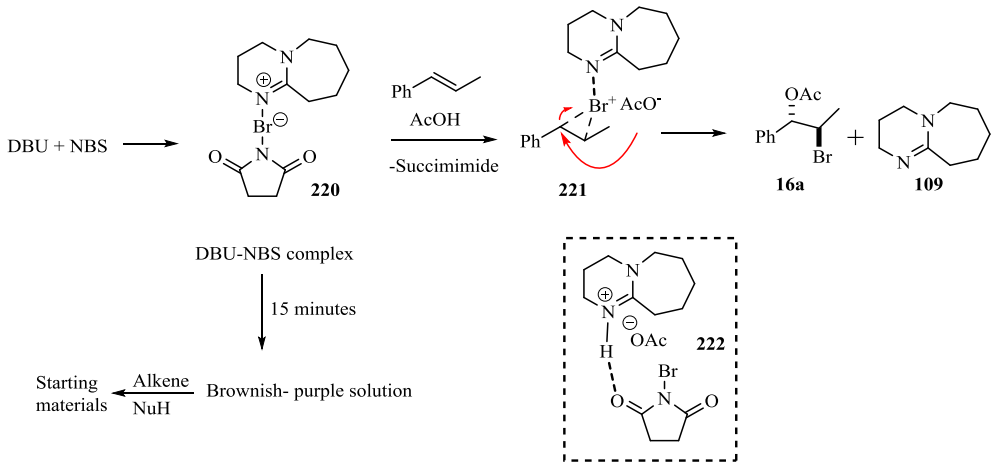


Figure 3.2 Proposed Mechanisms for Bromoacetoxylation Reaction.

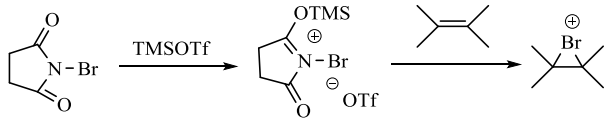
Although attempted crystallization DBU-NBS complex in CH_2Cl_2 and $CDCl_3$ failed, the conversion of mixture into brownish-purple solution after 15 minutes suggested the formation of new species in the reaction. This was further confirmed by the control experiment where brownish-purple solution did not catalyze the haloacetoxylation reaction probably due to the poisoning of catalyst after certain time.

The necessity of acidic condition for the halofunctionalization reactions was confirmed by our control experiments where halo etherification of *trans*-β-methyl styrene **15** with methanol and NBS failed (**Table 3.5**, entry 1). Although, the reaction promoted in the presence of stoichiometric amounts of acetic acid and excess amounts of methanol, significant formation of haloacetoxylation by-product limited their synthetic utility. The use of non-nucleophilic citric acid ceased the side reaction affording bromoetherification products in excellent yields.

Rationalization of the observed reactivity in halofunctionalization reactions required the identification of reactive species involved in the reactions. Although, isolation of the intermediate formed in the DBU catalyzed halofunctionalization reaction was unsuccessful, an intermediary of haloamidinium ion was proposed in the reactions (**Figure 3.2**). We assumed that DBU formed 1:1 complex with NXS during the reaction and H^+ sources was necessary for the liberation of haloamidinium ion which subsequently transferred X^+ ion to alkene and formed halonium ion intermediate. All of these experiments confirmed that the formation of halonium ion intermediate is a rate determining step and the catalytic activity was operated only in the presences of Brønsted acid. This was further confirmed by the bromofunctionalization of *trans*-β-methyl styrene with various nucleophiles (e.g., RO^-, RS^-, PhS^- and RSO_3^-) proceeded only in the presence of acids of corresponding nucleophiles.

The failure halofunctionalization reaction of unsaturated esters using our catalytic system but successful reaction in the presence of stoichiometric amounts of Lewis acid (i.e., TMSOTf) suggested the involvement of new reactive species in the halofunctionalization reactions. The newly formed reactive intermediate was expected as TMSOTf salts of *N*-bromosuccinimide (i.e., **217**) which transferred Br^+ ion to the double bond of enoates and formed the corresponding bromonium ion intermediates. Cleavage of the thioenoate bond in the presence of TMSOTf reflect the weak C-S bond while the failured halofunctionalization reactions of N-Boc-2-pyridone probably due to the less reactive nature of the substrate.

Scheme 3.31 NBS-TMSOTf (1:1) Complex and Bromonium ion Formations.

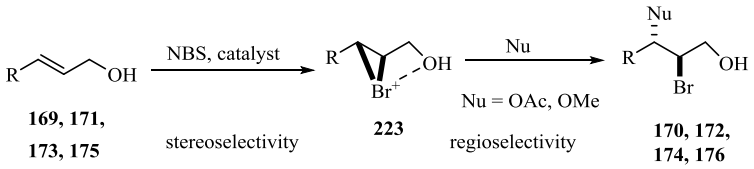


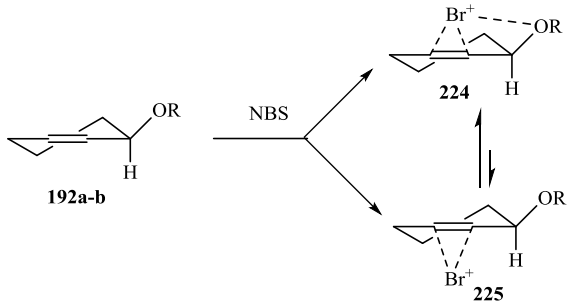
223

active interrmediate

Not surprisingly, DBU catalyzed bromoacetoxylation and bromoetherification reactions of electron rich double bond in an acyclic allyl alcohol with high yields and excellent regio- and diastereoselectivity. As suggested by Bellucci and coworkers,[112] coordination of the hydroxyl group with the bromonium ion intermediate in the electrophilic addition favor the *syn* attack to -OH group and gave transition state **223** which in fact controlled the stereoselectivity of the process (**Scheme 3.32**). Once the *syn*-bromonium ion intermediate **223** was formed, the OH group directed the nucleophilic attack at a carbon away from it via inductive effect thereby controlled the regioselectivity of the process. However in cyclic allyl alcohol, the addition of Br^+ ion leads to conformations **224** or **225**. Although, conformation **225** has lower dipole moment, the face of alkene *syn* to the oxygen substituent in conformation **195a-b** was more reactive due to the interaction of lone pairs electrons present in the oxygen with olefinic P-electron cloud and with the incoming Br^+ ion and gave conformation **224** as major intermediates. In the next step, "-OR" functional group directed the attack of the nucleophile at more electron deficient β-carbon of bromonium ion intermdeiate and controlled the regioselectivity. However, this rationalization demanded more experimental and theoretical studies.

Scheme 3.32 Transition State Models for the Regio- and Diastereocontrol Halofunctionalization Reactions of Allyl Alcohols.[112]





The lacks of enantioselectivity in inter- and intramolecular halofunctionalization reaction was probably due to the non-rigid nature of the organocatalyst employed for the reaction. We assumed that when catalytic systems interact with *N*-halo sources, the catalyst-X^+-alkene unit in the initial complex or in the transition state holds a linear arrangement. In this arrangement, ligand and alkene units can undergo 360 degree rotation about the halogen center of the triad and that gives several closely lying transition states for the nucleophilic attack. Now, the asymmetric ligand can be placed in the four quadrants of the ethylene structure where each position occupies one quadrant of space. For high enantioselectivity, asymmetric catalyst should discriminate two sets of quadrants in contrast to the remaining two. For examples in **Figure 3.3**, the attack of the nucleophile via quadrant A or C leads to one enantiomer, while attack from B or D lead to opposite enantiomer. The lack of enantioselectivity in the reaction was expected due to the absences of discrimination of nitrogen and phosphorus catalysts during the attack of the nucleophiles.

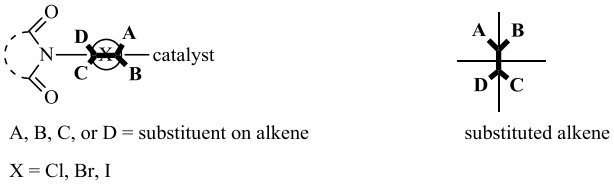


Figure 3.3 Transition State Model for Enantiocontrolled Attack on NBS-alkene-catalyst Complex.

Finally, formation of free halonium ions as intermediate along the alkene co-functionalization reaction coordinate provides a racemization pathway since exchange of X^+ between the halonium ion and starting alkene has been shown to be diffusion controlled in halogenation reactions (i.e., X_2).[13] The literature precedents for enantioselectivities up to 99% ee for scalemic amine•X^+ complex promoted halolactonization,[28, 61, 63-66] halocyclization[3] and the dependence of enantioselectivity on chiral amine and reaction mode (e.g., endo vs, exo cyclization)[60] suggested the viability of the approach. The syntheses of rigid imines based catalysts and examining their physical and computational properties may uncover new methodology for inter and intramolecular enantioselective alkene co-functionalization reactions in future.

3.7 Conclusion

In summary, several nitrogen and phosphorus organocatalyst (**109, 139-148, 154-158**) effectively catalyze the NBS, DBDH or NIS promoted halofunctionalization reaction of functionalized and non-functionalized alkenes in high yields, regio- and diastereoselectivity. It was confirmed from our investigation that C=N bond of imines acted as an efficient catalyst for the transfer of X^+ (usually Br^+ or I^+) ion from *N*-halonium sources to alkene during the halofunctionalization reaction. In our continued effort on exploring new organocatalyst for halofunctionalization reactions, imidazolium salts, chiral phosporamidite and chiral diphenylprolinol silyl ether were explored as new catalysts for these general set of reactions. In future, catalytic enantioselective halofunctionalization reaction of alkenes employing new nitrogen and phosphorus based chiral organocatalysts can be carried out for the asymmetric syntheses of halofunctionalized moiety present in several natural products.

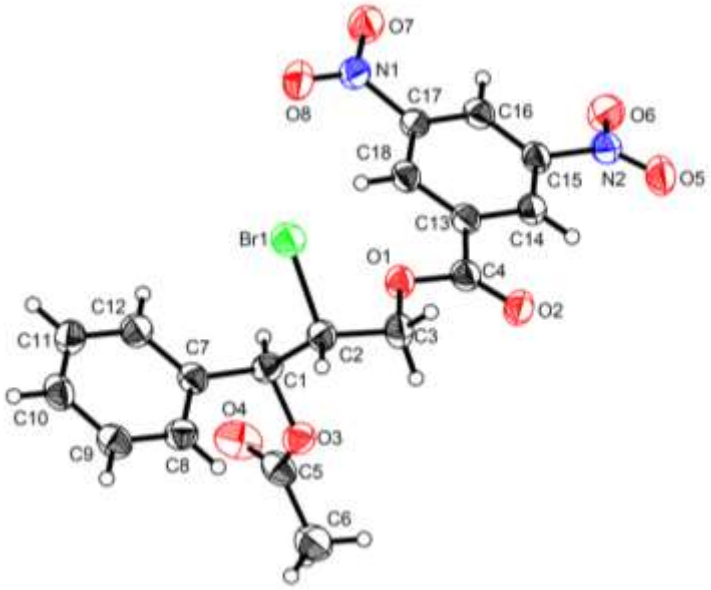


Figure 3.4 50% Probability Thermal Ellipsoids of **181**.

Table 3.9 Crystal Data and Structure Refinements for **181**.

Empirical formula	$C_{18}H_{15}Br\ N_2O_8$	
Formula weight	467.23	
Temperature	292 K	
Wavelength	0.7107 A	
Crystal system,	Prism	
SG	P2(1)/c	
Unit cell dimensions	a = 11.502 (2) Å	α = 90.00°
	b = 18.762 (4) Å	β = 107.48 (3)°
	c = 9.2104 (18) Å	γ = 90.00°
Volume	1895.9 (7) $Å^3$	
Z, calculated density	4, 1.637 Mg/m^3	
Absorption coefficient	2.219 mm^{-1}	
F (000)	944	
Crystal size	0.10 x 0.05 x 0.05 mm^3	
Theta range for data	1.8562 to 26.3520°	
Index ranges	-14<=h<=14, -23<=k<=23, -8<=l<=11	
Reflns col./unique	15667 / 3826 [R(int) = 0.0440]	
Completeness	99.3 %	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3826/0/262	
Goodness-of-fit on F^2	1.085	
Final R indices [I>2sigma (I)]	R1 = 0.0490, wR2 = 0.1241	
R indices (all data)	R1 = 0.0560, wR2 = 0.1320	
Largest diff. peak and hole	0.805 and -0.593 $e.A^{-3}$	

3.8 Experimental

General: NMR spectra were recorded as $CDCl_3$ or C_6D_6 solutions on a 300 or 500 MHz NMR instrument. The ^1H NMR chemical shifts were reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ = 0.00) or $CHCl_3$ (δ = 7.28) or C_6H_6 (δ = 7.16) as internal standard. The ^{13}C NMR chemical shifts were reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to the $CDCl_3$ signal (triplet, centerline δ = 77.0 ppm) or C_6D_6 signal (multiplet, centerline δ = 128.4 ppm). Infrared (IR) spectra were recorded as neat samples (liquid films on NaCl plates). Gas chromatography-mass spectrometry measurements were performed on a GC coupled to a quadruple detector at 70 eV. Analytical thin layer chromatography (TLC) was performed on silica gel plates, 200 μ mesh with F_{254} indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of phosphomolybdic acid. Flash chromatography was performed with 230-400 mess neutral alumina. The yields are of the materials isolated by column chromatography. The enantiomeric excess was determined by chiral HPLC analysis on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenyl carbamate) on silica gel].

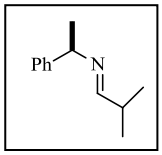
Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were distilled from sodium benzophenone ketyl. ^{n}BuLi (2.5 M in hexane) was commercially available and titrated using *sec*-butyl alcohol and 1,10-phenantroline monohydrate in THF. PhMgBr (2.8 M in Et_2O), vinyl magnesium bromide (1.0 M in THF) were titrated using menthol and 1,10-phenanthroline monohydrate in THF. All glassware's were flamed-dried under high vacuum and purged with argon before cooling under a dry nitrogen atmosphere. Low temperature baths (up to -78 ^oC) were prepared using thermoflasks with dry ice-isopropyl alcohol slush bath

mixtures or ice-NaCl (-23 ^{o}C) mixture. All reactions were conducted under a positive, dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

4-*tert*-butyl styrene, *trans*-*β*-methyl styrene, *cis*-*β*-methyl styrene, 4-methoxy styrene, *trans*-stilbene, cyclohexene, cycloheptene, methyl crotonate, ethyl sorbate, cinnamyl alcohol, 4-pentanoic acids and phenyl allyl ethers were commercially available and used directly for the reactions. *N*-chloroosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), and 1,3-dibromo-3,5-demethylhydantoin (DBDMH) were also commercially available and used for reaction without any purification. 1,5-diazobicyclo-[4.5.0]-undec-7-ene (DBU) was commercially available and used for the reactions. Ligands **143-151** were synthesized by using the literature procedure.

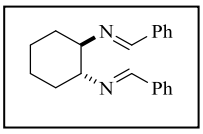
General Procedure A: Syntheses of Schiff Bases 143-146. The Schiff bases (aldimines and ketimines) used for our study were synthesized by the slight modification of literature procedure.[124] To the solution of aldehyde or ketone (1.0 equiv) in ethanol or toluene were added amines (1.05 equiv), oven dried (400 ^{o}C for 2 hours) 5 Å molecular sieves (2-3 gm) and the resulting mixture was refluxed for 4-24 hours. The reaction mixture was next cooled to room temperature and solvent was removed using rota vacuo. The pale yellow liquid was diluted with CH_2Cl_2, washed subsequently with saturated aqueous NH_4Cl solution and saturated aqueous brine solution. Organic layer was separated, dried over anhydrous magnesium sulfate, filtered and solvent was evaporated in rota vacuo. The purification of resulting pale yellow liquid using Kugelrohr vacuum distillation gave colorless solution of Schiff bases.

(*R*)–*N*-(1-Phenylethyl)-2-methyl-propanimine (139). Employing general procedure A and using



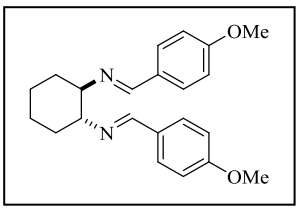
iso-butanaldehyde (360 mg, 5.0 mmol), (*S*)-(-)-1-phenylethylamine (606 mg, 5.05 mmol), oven dried 5Å molecular sieves (0.5 gm), EtOH (20.0 mL) gave **139** (822 mg, 94%) as a colorless liquid after purification by Kugelrohr vacuum distillation. ^{1}H and ^{13}C NMR data were identical to the literature report.[125]

***N,N*-Dibenzylidene-(*R,R*)-1,2-diaminocyclohexane (140).** Employing literature procedure and



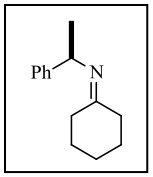
refluxing the mixture of 1,2-diaminocyclohexane (1.14 gm, 10.0 mmol), benzaldehyde (2.12 gm, 20.0 mmol), K_2CO_3 (10 mg) in ethanol gave **140** as orange color crystal in quantitative yields. The identification of the compound was carried out on comparing with literature data.[126]

***N,N*-Dibenzylidene-(*R,R*)-1,2-diaminocyclohexane (141).** Employing literature procedure[127]



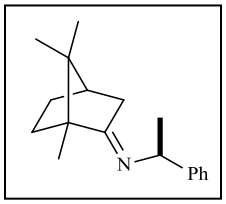
and refluxing the mixture of 1,2-diaminocyclohexane (1.14 gm, 10.0 mmol), 4-anisaldehyde (2.72 gm, 20.0 mmol), K_2CO_3 (10 mg) in ethanol gave compound 1**41** as orange color crystal in quantitative yields. The identification of the compound was carried out on comparing with literature data.[127]

(*R*)-*N*-(1-phenylethyl)cyclohexanimine (142). Employing general procedure A and using



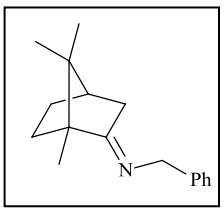
cyclohexanone (490 mg, 5.0 mmol), (*S*)-(-)-1-phenylethylamine (606 mg, 5.05 mmol), oven dried 5Å molecular sieves (0.5 gm), EtOH (20.0 mL) and refluxing resulting the mixture for 4 hours gave **142** (935 mg, 93%) as a colorless liquid after purification by Kugelrohr vacuum distillation. ^{1}H and ^{13}C NMR data were identical to the literature report.[124]

(*R*)-*N*-(1-phenylethyl)bornanimine (143).[128] Employing general procedure A and using



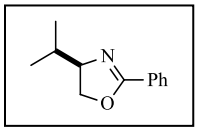
camphor (760 mg, 5.0 mmol), (*S*)-(-)-1-phenylethylamine (606 mg, 5.05 mmol), oven dried 5Å molecular sieves (0.5 gm) in toluene (20.0 mL) and refluxing the resulting mixture for 24 hours gave **143** (1.11 gm, 87 %) as a colorless liquid after purification by Kugelrohr vacuum distillation. ^{1}H and ^{13}C NMR data were identical to literature report.[129]

***N*-benzylbornanimine (144).** Employing general procedure A and using camphor (760 mg, 5.0



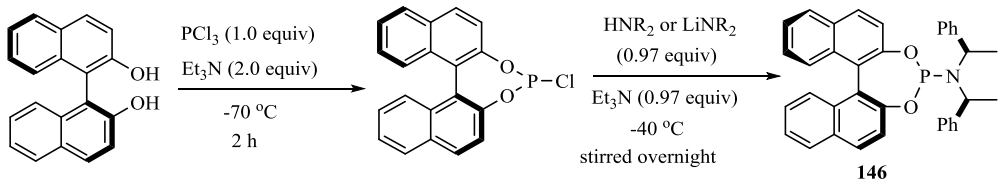
mmol), benzyl amine (541 mg, 5.05 mmol) and oven dried 5Å molecular sieves (1.0 gm) in toluene (20.0 mL) gave pure **144** (1.07 gm, 89%) as colorless oil after purification by Kugelrohr vacuum distillation. ^{1}H NMR and ^{13}C NMR data were identical to literature report.

4-(*R*)-4,5-Dihydro-4-(1-methylethyl)-2-phenyl oxazole (145). Dihydrooxazole **145** was



synthesized by the slight modification of the literature procedure.[130] To the solution of L-leucinol (117 mg, 1.0 mmol) in methanol (5.0 mL) was added benzaldehyde (106 mg, 1.0 mmol) at room temperature and the resulting mixture was heated at 45 ^{o}C for 12 hours. Solvent was evaporated in the rota vacuo and the remaining pale yellow liquid was dissolved in CH_2Cl_2 (20.0 mL). Silver oxide (232 mg, 1.1 mmol) was added and the resulting mixture was stirred for 5 hours at room temperature. The reaction mixture was filtered, filtrate was concentrated in the rota vacuo and purified using flash column chromatography (silica, 10-15% EtOAc in petroleum ether, v/v) gave **145** (146 mg, 77%) as a colorless oil. The ^{1}H and ^{13}C NMR spectrum of the product were identical to literature data.[131]

***O,O'*-(*S*)-(1,1'-dinapthyl-2,2'-diyl)-*N,N'*-di-(*S,S*)-1-phenylethylphosphoramidite (146).** Phosphoramidite ligand **146** was synthesized using the modified Feringa's procedure.[132] Treatment of (*S*)-2,2'-binaphthol (1.0 equiv) with PCl_3 (1.0 equiv) and Et_3N (2.0 equiv) in toluene at -70 ^oC furnished binaphthol phosphoryl chloride by filtration under argon atmosphere. Binaphthol phosphoryl chloride was added to Et_3N (0.99 equiv) and (+)-*bis*[(*R*)-1-phenylethyl]amine (0.99 equiv) at -40 ^oC and after additional 16 hours of stirring, phosphoramidite **146** was attained in modest chemical yield after purification by flash chromatography (38-40%).

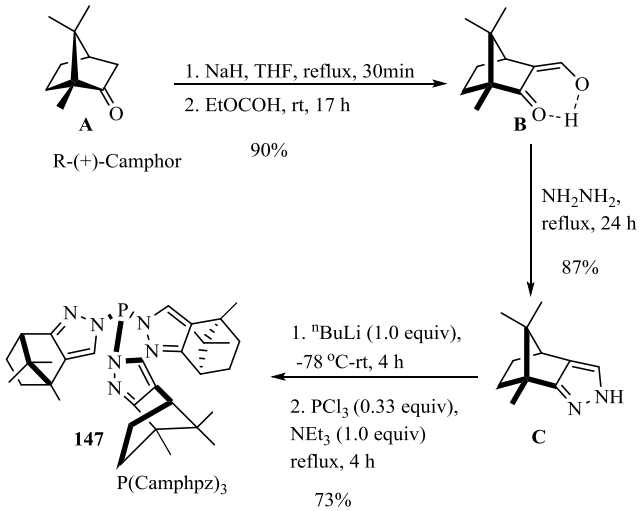


Syntheses of *tris*-[(4S,7R)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl] phosphine (147). The C_3 symmetric chiral *tris*-[(*4S,7R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl] phosphine (**147**) was synthesized by using the slight modification of literature procedure in three steps.[133] To the solution of *R*-(+)-camphor (1.52 g, 10.0 mmol) in anhydrous THF (30.0 mL) was added sodium hydride (1.2 g, 50.0 mmol) under argon and the resulting mixture was stirred for 15 minutes at room temperature. The reaction mixture was next refluxed for 15 minutes, cooled to room temperature and ethyl formate (2.86 gm, 40.0 mmol in 10.0 mL THF) was added over 2 hours. The resulting mixture was stirred for 16 hours at room temperature before quenching with isopropyl alcohol (10.0 mL). The reaction mixture was acidified until pH 1 using concentrated HCl, extracted with Et_2O (3 x 20.0 mL), organic layer was washed with saturated brine solution (20.0 mL), dried over anhydrous $MgSO_4$ and solvent removal using rota vacuo gave 3-(hydroxymethylene)-1,7,7-trimethylbicyclo [2.2.1] hexan-2-one

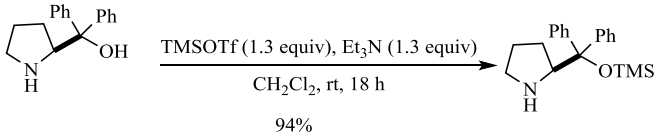
B (1.62 gm, 90%) as a pale yellow solid. The identification of product was carried out by comparing their NMR and IR data with literature results.[134]

The pale yellow product **B** obtained in the above reaction was used for the next reaction without purification. To the solution of **B** (900 mg, 5.0 mmol) in methanol (20.0 mL) was added hydrazine (160 mg, 5.0 mmol) at room temperature and the resulting mixture was refluxed for 24 hours. Evaporation of solvents followed by recrystallization of resulting solid in acetone gave pale yellow (*4S,7R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazole (**C**) as pale yellow solid (766 mg, 87%). The identification of the product was carried out on comparing their NMR data with literature data.[134] **C**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.64 (s, 3H), 0.95 (s, 3H), 1.11-1.17 (m, 1H), 1.30 (s, 3H), 1.80-1.87 (m, 1H), 2.03-2.10 (m, 1H), 2.28 (d, J = 7.3 Hz, 1H), 3.48 (d, J = 4.6 Hz, 2H), 7.07 (d, J = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 19.2, 20.4, 27.8, 33.6, 47.0, 50.0, 61.0, 120.0, 126.0, 166.1.

Finally the chiral tripod ligand *tris*-[(4S,7R)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl] phosphine (**147**) was synthesized by the modification of literature procedure.[135] To the stirred solution of **C** (263 mg, 1.5 mmol) in dry THF was added ^{n}BuLi (0.6 mL, 2.5 M in THF, 1.5 mmol) at -78 ^{o}C and the resulting reaction mixture was warmed to the room temperature over 4 hours. The reaction mixture was again cooled down to -78 ^{o}C followed by slow addition of PCl_3 (69 mg, 0.5 mmol) was carried out. The reaction mixture was warm up to room temperature over 4 hours before refluxing for 5 hours. The evaporation of solvent gave **147** (203 mg, 73%) as pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (br s, 9H), 0.91 (br s, 9H), 1.29 (br s, 9H), 1.30-2.12 (m, 12H), 2.86 (br s, 3H); 7.25 (br s, 6H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 19.0, 20.2, 27.6 (br), 33.5 (br), 47.1 (br), 51.0, 62.2, 122.1, 127.1, 162.8.

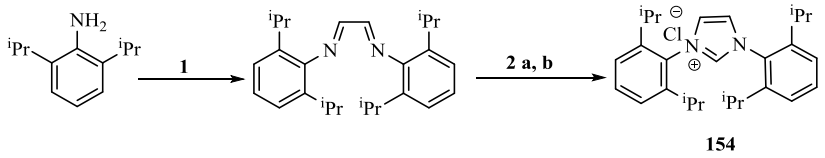


Diphenyl-2-prolinol trimethylsilyl ether (148): Compound **148** was synthesized by using the literature procedure.[136] To the solution of diphenyl-2-prolinol (235 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) was added TMSOTf (289 mg, 1.3 mmol) and Et_3N (132 mg, 1.3 mmol) and the resulting reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was quenched with water (5.0 mL), extracted with CH_2Cl_2 (3 x 10.0 mL) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 x 10.0 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in rota vacuo. Purification of product using flash column chromatography (silica, 40% EtOAc in petroleum ether, v/v) gave pure **148** (306 mg, 94%) as a colorless oil. The ^1H and ^{13}C NMR spectrum of the product were identical to the literature data.[136]



1,3-Bis-(2,6-diisopropylphenyl)-imidazolium chloride (154). Imidazolium salt **154** was synthesized in two steps by using the literature procedure.[103] The first step involved refluxing the mixture of 2,6-diisopropylaniline (19.7 gm, 2.0 equiv) with glyoxal (7.25 gm, 1.0 equiv) in methanol in the presence of catalytic amounts of acetic acid for 10 h. The resulting mixture was

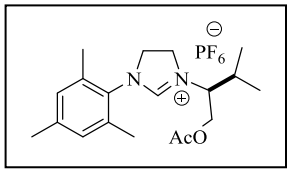
filtered and the residue was washed with ice cold methanol (3 x 20.0 mL) followed by oven drying gave 1,4-diaryl-1,4-diazadienes (DADs) as a pale yellow solid. In the second step, TMSCl (3.82 mL in 10.0 mL EtOAc, 30.3 mmol) was added to the mixture of DADS product (11.3 gm, 30.0 mmol) and paraformaldehyde (0.90 g, 30.3 mmol) in EtOAc (150.0 mL) at 70°C over 45 min. The resulting yellow suspension was stirred for 2 hours at 70 °C before cooling to 10 °C. The suspension was filtered and the residue was washed with the mixture of EtOAc and ^{t}BuOMe (40.0 mL, 1:1 ratio). The drying of solid in oven for 24 hours gave **150** (9.1 gm, 78%) as pale yellow solid. ^{1}H and ^{13}C NMR spectra of of imidazolium salt were identical to the literature data.[103]



154

1. Glyoxal, AcOH, MeOH, 50 ^{o}C, 10 h, 86% **2 a.** paraformaldehyde, EtOAc, 70 ^{o}C, 2 h **b.** TMSCl in EtOAc, 78%

1-((*1s*)-1-Acetoxymethyl-2-methylpropyl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-3H-imidazol-1-ium hexafluorophosphate (156). The imidazolium salt **155** was prepared using literature procedure[104] and employed for the next step. The –OH protection of imidazolium salt **155** was carried out using modified literature procedure. To the solution of imidazolium salt **155** (419 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) was added acetic anhydride (250 mg, 2.5 mmol) and

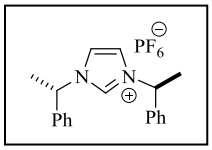


DMAP (369 mg, 3.0 mmol) and the resulting mixture was stirred for 3 hours at room temperature. The reaction mixture was diluted with water (5.0 mL), extracted with CH_2Cl_2 (3 x 10.0 mL), organic phase was dried over $MgSO_4$, filtered and solvent evaporated in rota vacuo. Purification of crude product by flash column chromatography (silica, 5-10% acetone in CH_2Cl_2, v/v) gave pure **156** (430 mg, 93%) as a crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (dd, J = 14.7, 6.9 Hz,

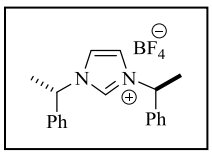
6H), 2.04 (s, 3H), 2.22 (s, 6H), 2.28 (s, 3H), 3.84-3.89 (m, 1H), 4.13-4.36 (m, 6H), 6.92 (s, 2H), 7.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.1, 18.7, 19.3, 20.4, 20.9, 26.8, 45.4, 50.7, 61.0, 63.9, 129.9, 130.1, 135.0, 140.4, 158.5, 170.4.

1,3-Bis- (1-(*R*)-phenylethyl)-imidazolium hexafluorophosphate (157). Imidazolium salt **157** was prepared using literature procedure.[105] To the solution of (*R*)-phenylethylamine (1.21 gm, 10.0 mmol) in toluene was added paraformaldehyde (300 mg, 10.0 mmol) at room temperature with vigorous stirring. After 30 minutes second equivalent of (*R*)-phenylethylamine (1.21 gm, 10.0 mmol) was added at 0 ^{o}C. Next, HCl (3.0 mL, 3.3 M) was added after 15 minutes. The reaction mixture was warmed up to room temperature over 30 minutes and glyoxal (2.8 gm, 40% in water) was added. Reaction mixture was stirred for 12 hours at 40 ^{o}C before quenched with saturated aqueous Na_2CO_3 solution (10.0 mL). Reaction mixture was extracted with CH_2Cl_2 (5 x 20.0 mL) dried over anhydrous $MgSO_4$, filtered and solvent was evaporated in rota vacuo.

The crude mixture was next dissolved in water (20.0 mL), KPF_6 (1.85 gm, 10.0 mmol) was added and mixture was stirred for 2 hours at room temperature. The reaction mixture was extracted with CH_2Cl_2 (3 x 20.0 mL) and the combined organic fraction was washed subsequently with brine (20.0 mL) and water (20.0 mL). Organic phase was dried over anhydrous $MgSO_4$, filtered and solvent was evaporated in rota vacuo. Recrystallization of crude product from CH_2Cl_2 and hexane solution gave compound **157** as orange color crystals (3.63 gm, 43 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (d, J =7.3 Hz, 6H), 5.63 (q, J = 6.4 Hz, 2H), 7.11 (d, J = 7.4 Hz), 7.31-7.37 (m, 10H), 8.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 60.3, 121.0, 126.9 (2-carbons), 129.5, 133.5, 137.4, 137.5.



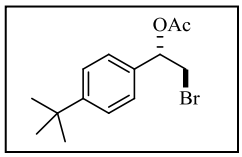
1,3-Bis-(1-(*R*)-phenylethyl)-imidazolium tetraflouroborate (158): Imidazolium salt **158** was



prepared using literature procedure.[105] To the solution of (*R*)-phenylethylamine (121 mg, 1.0 mmol) in toluene was added paraformaldehyde (30 mg, 1.0 mmol) at room temperature with vigorous stirring. After 30 minutes second equivalent of (*R*)-phenylethylamine (121 mg, 1.0 mmol) was added at 0 ^{o}C. Under constant stirring, HBF_4 (1.0 mmol) was added. After 15 minutes, glyoxal (58 mg, 1.0 mmol) was added slowly at room temperature and the resulting mixture was stirred for 12 hours at 40 ^{o}C. The reaction mixture was diluted with saturated aqueous Na_2CO_3 solution, aqueous phase was extracted with CH_2Cl_2 (3 x 10.0 mL). Combined organic layer was washed subsequently with brine (10.0 mL) and water (10.0 mL), dried over anhydrous $MgSO_4$, filtered and concentration in rota vacuo. The crude product was pure enough to use for the next reaction. The identification of product was carried out on comparing their NMR with literature data.[105]

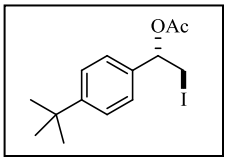
General Procedure B: Representative procedure for the halofunctionalization of alkene using *N*-halosuccinimide. To the stirred solution of alkene (1.0 mmol) in CH_2Cl_2 (5.0 mL) under argon was added the *N*-halosuccinimide (NBS or NIS, 1.0 mmol), catalyst (2-10 mol%) and nucleophile (1.0 mmol). The resulting mixture was stirred at room temperature for 2-12 hours before quenching with saturated aqueous sodium sulfite solution, diluted with water and extracted using CH_2Cl_2 (3 x 10.0 mL). The combined organic layer was washed with saturated aqueous NH_4Cl solution, dried over anhydrous $MgSO_4$, filtered, concentrated in rota vacuo and purified using flash column chromatography (neutral alumina, 5-15 % CH_2Cl_2:petroleum ether, v/v).

(1S*) 1-Acetoxy-1-(4-*tert*-butylphenyl)-2-bromoethane (137). Employing general procedure B



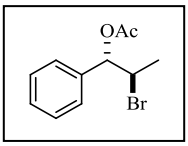
and using 4-*tert*-butylstyrene (160 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU or aldimine or ketimine (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 5-10% CH_2Cl_2 in petroleum ether, v/v) gave pure **137** (86-95%) as a colorless oil: IR (neat) 2964 (s), 1749 (s), 1371 (s), 1237 (br s), 1019 (s), 780 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9 H), 2.15 (s, 3H), 3.58-3.69 (m, 2H), 5.99 (dd, J = 8.7, 4.6 Hz, 1H), 7.29-7.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 31.2, 34.3, 34.6, 74.7, 125.6, 126.3, 134.6, 151.8, 179.9; mass spectrum *m/z* (relative intensity) EI 300 (0.24, M^+), 298 (0.25, M^+), 241 (3), 240 (4), 239 (3), 238 (4), 219 (23), 218 (44), 203 (46), 177 (38), 176 (100), 163 (80), 161 (52), 159 (59), 145 (33), 117 (17), 105 (10), 91 (20), 77 (9), 57 (32). HRMS (EI) calculated for $[C_{14}H_{19}BrO_2]^+$: 298.0568, found 298.0572.

(1S*) 1-Acetoxy-1-(4-*tert*-butylphenyl)-2-Iodoethane (138). Employing general procedure B



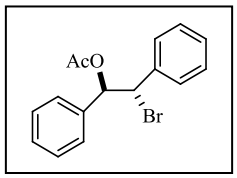
and using 4-*tert*-butylstyrene (160 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (2 mol%), AcOH (60 mg, 1.0 mmol) after purification by flash chromatography (neutral alumina, 5-10% CH_2Cl_2 in petroleum ether, v/v) gave pure **138** (336 mg, 97%) as a colorless oil: IR (neat) 2963 (s), 2875 (s), 1747 (s), 1370 (s), 1233 (s), 1057 (s), 1017 (s), 605 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.15 (s, 3H), 3.45-3.52 (m, 2H), 5.90 (dd, J = 8.3, 5.1 Hz, 1H), 7.28-7.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 21.0, 31.2, 34.6, 75.1, 125.6, 126.1, 135.4, 151.7, 169.8; mass spectrum *m/z* (relative intensity) EI 346 (0.26, M^+), 220 (15), 219 (92), 203 (24), 178 (10), 177 (27), 163 (61), 159 (100), 145 (64), 128 (17), 117 (32), 115 (17), 105 (17), 91 (27), 77 (13), 57 (67).

(1S*, 2R*) 1-Acetoxy-1-phenyl-2-bromopropane (16a). Employing general procedure B and



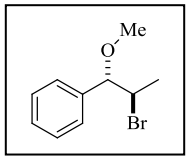
using *trans*-β-methylstyrene (118 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU or aldimine or ketimine (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature after purification by flash chromatography (neutral alumina, 5-10% CH_2Cl_2 in petroleum ether, v/v) gave pure **16a** (79-97%) as a colorless oil. ^{1}H NMR and ^{13}C NMR data were identical to literature report.[15]

(1R*, 2S*) 1-Acetoxy-1-phenyl-2-bromo-2-phenyl ethane (13). Employing general procedure



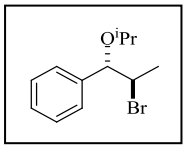
B and using *trans*-stilbene (180 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), aldimine or ketimine (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 5-10% CH_2Cl_2 in petroleum ether, v/v) gave pure **13** (205 mg, 64%) as a colorless oil. ^{1}H NMR and ^{13}C NMR data are identical to literature report.[15]

(1S*,2R*) 1-Methoxy-1-phenyl-2-bromopropane (16b). Employing general procedure B and



using *trans-β*-methylstyrene (118 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), methanol (64 mg, 2.0 mmol), DBU (2 mol%), citric acid (0.34 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 10-15 % CH_2Cl_2: petroleum ether, v/v) gave pure compound **16b** (75-90%). ^{1}H NMR and ^{13}C NMR data are identical to literature report.[137]

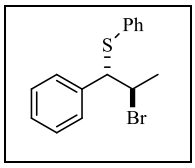
(1S*,2R*) 1-(1-Methylethoxy)-1-phenyl-2-bromopropane (16c). Employing general procedure



B and using *trans-β*-methylstyrene (118 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), isopropyl alcohol (120 mg, 2.0 mmol), DBU (2 mol%), citric acid monohydrate (74 mg, 0.34 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 10-15% CH_2Cl_2 in petroleum ether, v/v)

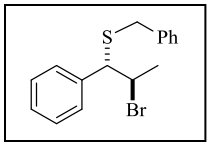
gave pure **16c** (219 mg, 85%) as a colorless oil: IR (neat) 2961 (s), 2872 (s), 1753 (s), 1366 (s), 1231 (s), 1058 (s), 1013 (s), 611 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.67 (d, J = 6.9 Hz, 3H), 3.57 (sext, J = 5.9 Hz, 1H), 4.20 (dq, J = 12.6, 6.4 Hz, 1H), 4.54 (d, J = 5.5 Hz, 1H), 7.29-7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.2, 23.2, 53.2, 70.4, 82.9, 127.4, 127.9, 128.1, 140.4; mass spectrum *m/z* (relative intensity) EI 258 (0.2, M^+), 256 (0.2, M^+), 199 (1), 197 (1), 149 (41), 117 (12), 107 (100), 91 (9), 79 (35), 77 (12), 51 (5). HRMS (EI) calculated for $[C_{12}H_{17}BrO]^+$: 256.0463, found: 256.0464.

(1S*,2R*) 1-Phenyl-1-thiophenyl-2-bromopropane (16d). Employing general procedure B and



using *trans-β*-methylstyrene (118mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), benzylthiol (1.24 g, 10.0 mmol), DBU (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 20-30% CH_2Cl_2 in petroleum ether, v/v) gave pure **16d** (206 mg, 67%) as a colorless oil: IR (neat) 2977 (s), 2911 (s), 2867 (s), 1402 (s), 1197 (s), 1038 (s), 719 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, J = 6.8 Hz, 3H), 3.59-3.61 (m, 1H), 4.29 (d, J = 5.9 Hz, 1H), 7.05-7.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 50.1, 59.5, 126.8, 127.3, 127.4, 128.2, 126.5, 128.7, 128.9, 131.7, 132.7, 140.1; mass spectrum *m/z* (relative intensity) EI 308 (0.19, M^+), 306 (0.18, M^+), 227 (100), 199 (45), 197 (44), 149 (84), 118 (27), 117 (66), 115 (32), 109 (21), 91 (22), 77 (10), 65 (15). HRMS (EI) calculated for $[C_{15}H_{15}BrS]^+$: 306.0078, found: 306.0076.

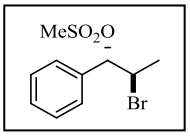
(1S*,2R*) 1-Phenyl-1-(thiophenylmethyl)-2-bromopropane (16e). Employing general



procedure B and using *trans-β*-methylstyrene (118 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), benzylthiol (1.24 gm, 10.0 mmol), DBU (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature, after

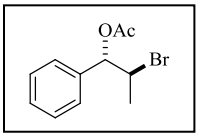
purification by flash chromatography (neutral alumina, 20-30% CH_2Cl_2 in petroleum ether, v/v) gave pure **16e** (180 mg, 56%) as a colorless oil: IR (neat) 2971 (s), 2919 (s), 2856 (s), 1409 (s), 1207 (s), 1033 (s), 737 (s), 719 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (d, J = 6.8, 3H), 2.82-2.87 (m, 1H), 3.24-3.45 (m, 2H), 3.68 (d, J = 6.9, 1H), 7.07-7.26 (m, 10H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 19.0, 35.5, 44.6, 55.1, 126.9, 127.3, 128.2, 128.3, 128.9, 129.1, 138.0, 140.2; mass spectrum *m/z* (relative intensity) EI 322 (0.4, M^+), 320 (0.4, M^+), 246 (6), 183 (5), 181 (5), 91 (100), 65 (12). HRMS (EI) calculated for $[C_{16}H_{17}BrS]^+$: 320.0234, found: 320.0233.

(1S*,2R*) 1-Methanesulfonyl-1-phenyl-2-bromopropane (16f). Employing general procedure



B and using *trans-β*-methylstyrene (118 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), methane sulfonic acid (192 mg, 2.0 mmol), DBU (3mg, 2 mol %) at room temperature, after purification by flash chromatography (neutral alumina, 10-15 % CH_2Cl_2 in petroleum ether, v/v) gave pure **16j** (264 mg, 90%, dr 100:0) as a colorless oil: IR (neat) 3030 (s), 2977 (s), 2935 (s), 1454 (s), 1361 (br s), 1175 (s), 952 (s), 844 (s), 701 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.79 (d, J = 6.9 Hz, 3H), 2.82 (s, 3H), 4.37 (dq, J = 13.3, 6.9 Hz, 1H), 5.65 (d, J = 5.9 Hz, 1H), 7.38-7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 39.1, 49.1, 86.5, 127.2, 128.8, 129.5, 135.8; mass spectrum *m/z* (relative intensity) EI 294 (0.51, M^+), 292 (0.46, M^+), 213 (10), 199 (8), 198 (11), 197 (8), 196 (10), 185 (59), 171 (12), 169 (12), 135 (8), 123 (20), 118 (59), 117 (100), 115 (41), 107 (94), 105 (17), 91 (37), 79 (38), 77 (26), 65 (10), 51 (18). HRMS (EI) calculated for $[C_{10}H_{13}BrO_3S]^+$: 291.9769, found 291.9768.

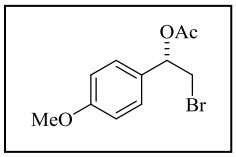
(1R*, 2S*) 1-Acetoxy-1-phenyl-2-bromoethane (151a). Employing general procedure B and



using *cis-β*-methylstyrene (118 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU or aldimine or ketimine (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature gave after purification by flash chromatography (neutral alumina, 5-10%

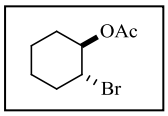
CH_2Cl_2 in petroleum ether, v/v) pure **151a** (75-89%) as a colorless oil: IR (neat) 2967 (s), 1743 (s), 1369 (s), 1239 (s), 1021 (s), 779 (s), 721 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56 (d, J = 6.0 Hz, 3H), 2.14 (s, 3H), 4.35 (dq, J = 14.2, 7.4 Hz, 1H), 5.85 (d, J = 7.8 Hz, 1H), 7.31-7.39 (m, 5H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 22.3, 50.6, 79.2, 127.2, 128.6, 128.7, 137.2, 169.6; mass spectrum *m/z* (relative intensity) EI 258 (0.05, M^+), 256 (0.04, M^+), 176 (15), 149 (64), 134 (19), 117 (32), 107 (100), 91 (11), 77 (16). The enantiomeric excess was determined by chiral HPLC analysis on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenyl carbamate) on silica gel] to be up to 15% ee (hexane/^{i}PrOH, 97:3 (v/v), flow rate = 1.0 mL/min, direction at λ = 254 nm, minor retention time = 6.49 mins, major retention time = 7.43 mins.

(1S*) 1-Acetoxy-1-(4-methoxyphenyl)-2-bromoethane (153). Employing general procedure B



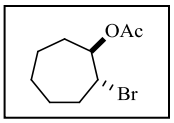
and using 4-methoxystyrene (134 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), aldimine or ketimine (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 5-10% CH_2Cl in petroleum ether, v/v) gave pure **153** (75-89%) as a colorless oil. ^1H NMR and ^{13}C NMR data are identical to literature report.[138]

(1R*,2R*) 1-Acetoxy-2-bromocyclohexane (6). Employing general procedure B and using



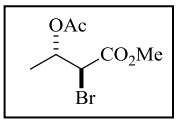
cyclohexene (82 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU or aldimine or ketimine (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 5-10% CH_2Cl_2 in petroleum ether, v/v) gave pure **6** (78-95%) as a colorless oil. ^1H NMR and ^{13}C NMR data are identical to literature report.[139]

(1R*,2R*) 1-Acetoxy-2-bromocycloheptane (160). Employing general procedure B and using



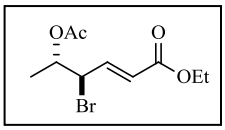
cycloheptene (96 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), ketimine (2 mol%), AcOH (60 mg, 1.0 mmol) at room temperature, after purification by flash chromatography (neutral alumina, 5-10% CH_2Cl_2 in petroleum ether, v/v) gave pure **160** (58-86%) as a colorless oil. ^{1}H NMR and ^{13}C NMR data are identical to literature report.[140]

(2S*,3S*) Methyl 2-bromo-3-acetoxy-2-butanoate (162). Employing general procedure B and



using methyl crotonate (100 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), AcOH (60 mg, 1.0 mmol) and trimethylsilyl trifluromethanesulfonate (TMSOTf, 222 mg, 1.0 mmol) after purification by fl1`ash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **162** (160 mg, 67%) as a colorless oil. ^{1}H NMR and ^{13}C NMR data were identical to literature report.[141]

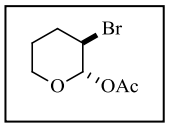
(4R*,5S*) Ethyl 4-bromo-5-acetoxy-2-hexenoate (164). Employing general procedure B and



using ethyl sorbate (140 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), AcOH (60 mg, 1.0 mmol) and trimethylsilyl trifluromethane-sulfonate (TMSOTf, 222 mg, 1.0 mmol) after purification by flash column chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **164** (223 mg, 80%) as a colorless oil: IR (neat) 2983 (s), 2931 (s), 1749 (s), 1722 (s), 1371 (s), 1229 (s), 1180 (s), 1032 (br s), 979 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 1.70 (d, J = 6.9 Hz, 3H), 2.17 (s, 3 H), 4.22 (q, J = 6.9 Hz, 2H), 4.19-4.24 (m, 1H), 5.51 (t, J = 4.6 Hz, 1H), 6.06 (dd, J = 15.6, 1.4 Hz, 1H), 6.89 (dd, J = 11.5, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 20.8, 21.2, 47.9, 60.8, 75.0, 124.8, 140.8, 165.4, 169.6; mass spectrum *m/z* (relative intensity) EI 280 (3.11, M^+), 278 (3.09, M^+), 237 (3), 235 (3), 221 (13), 219 (14), 199 (10), 192 (29), 191 (30), 171

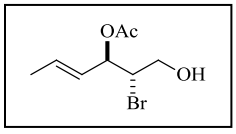
(45), 157 (100), 153 (54), 139 (20), 129 (50), 111 (83), 101 (24), 95 (16), 83 (41), 65 (14), 55 (29).

(2R*,3R*) 2-Acetoxy-3-bromo-pyran (168). Employing general procedure B and using 2,3-



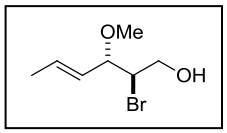
dihydropyran (84 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (2 mol%), AcOH (60 mg, 1.0 mmol) in CH_2Cl_2 after purification by flash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **168** (167 mg, 75%) as a colorless oil: IR (neat) 2953 (s), 2887 (s), 1735 (s), 1404 (s), 1238 1013 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.58-1.71 (m, 1H), 1.93-2.07 (m, 2H), 2.13 (s, 3H), 2.38-2.45 (m, 1H), 3.71-3.76 (m, 1H), 3.96-4.02 (m, 2H), 5.86 (d, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 23.4, 30.4, 47.3, 64.5, 94.4, 169.2; mass spectrum *m/z* (relative intensity) EI 224 (0.01, M^+), 222 (0.01, M^+), 165 (100), 163 (100), 123 (7), 121 (8), 84 (82), 83 (58), 55 (99).

(2S*,3R*) 2-Bromo-3-acetoxy-4-hexen-1-ol (170a). Employing general procedure B and using



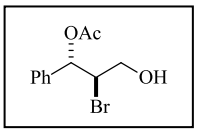
2,4-hexadiene-1-ol (98 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3 mg, 2 mol%), AcOH (60 mg, 1.0 mmol) in CH_2Cl_2 at 0 ^oC for one hour after purification by flash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure compound **170a** (202 mg, 85%) as a colorless oil: IR (neat) 3431 (br s), 2964 (s), 1737 (s), 1451 (s), 1353 (s), 1066 (s), 737 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75 (d, J = 6.0 Hz, 3H), 2.11 (s, 3H), 3.81-3.86 (m, 2H), 4.19-4.23 (m, 1H), 5.47-5.49 (m, 1H), 5.52-5.57 (m, 1H), 5.85-5.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 21.1, 57.5, 63.6, 74.1, 125.6, 133.1, 169.9; mass spectrum *m/z* (relative intensity) EI 238 (0.2, M^+), 236 (0.2, M^+), 209 (14), 207 (14), 127 (17), 99 (100), 85 (23). HRMS (EI) calculated for $[C_8H_{13}BrO_3]^+$: 236.0048, found 236.0047.

(2S*,3R*) 2-Bromo-3-methoxy-4-hexen-1-ol (170b). Employing general procedure B and using



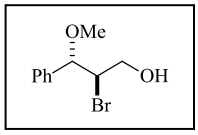
2,4-hexadiene-1-ol (98 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3 mg, 2 mol%), methanol (160 mg, 5.0 mmol), citric acid monohydrate (74 mg, 0.33 equiv) in CH_2Cl_2 after purification by flash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **170b** (173 mg, 83%) as a colorless oil: IR (neat) 3466 (br s), 3041 (s), 2947 (s), 1431 (s), 1347 (s), 1225 (s), 1031 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.79 (dd, J = 6.4, 1.4 Hz, 3H), 2.4 (br s, 1H), 3.32 (s, 3H) 3.80-3.96 (m, 3H), 4.07 (q, J = 5.5 Hz, 1H), 5.40 (dd, J = 8.3, 6.9 Hz, 1H), 5.80 (dq, J = 15.1, 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 56.6, 57.2, 64.7, 84.3, 127.7, 132.5; mass spectrum *m/z* (relative intensity) EI 210 (0.1, M^+), EI 208 (0.1, M^+), 86 (6), 85 (100), 67 (5), 55 (22).

(2R*,3R*) 1-Acetoxy-1-phenyl-2-bromo propan-1-ol (172a). Employing general procedure B

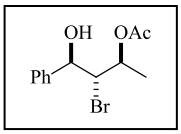


and using cinnamyl alcohol alcohol (134 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3 mg, 2 mol%), AcOH (60 mg, 1.0 mmol) in CH_2Cl_2 after purification by flash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **172a** (224 mg, 82%) as a colorless oil: IR (neat) 3450 (br s), 3040 (s), 2958 (s), 1742 (s), 1454 (s), 1367 (s), 1238 (br s), 1045 (s), 763 (s), 702 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.77 (s, 1H), 4.34 (dd, J = 11.9, 4.1 Hz, 1H), 4.44-4.47 (m, 1H), 4.53 (dd, J = 11.9, 6.9 Hz, 1H), 5.03 (d, J = 5.5 Hz, 1H), 7.33-7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 55.6, 64.1, 74.9, 126.4, 128.4, 128.5, 139.4, 170.5; mass spectrum *m/z* (relative intensity) EI 274 (0.33, M^+), 272 (0.35, M^+), 195.3 (4), 149 (13), 133 (57), 108 (12), 107 (100), 106 (37), 105 (61), 91 (10), 79 (69), 77 (41), 61 (19), 55 (9), 51 (11). HRMS (EI) calculated for $[C_{11}H_{13}BrO_3]^+$: 272.0048, found 272.0048.

(2R*,3R*) 1-Methoxy-1-phenyl-2-bromo propan-1-ol (172b). Employing general procedure B and using cinnamyl alcohol alcohol (134 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3 mg, 2 mol%), methanol (160 mg, 5.0 mmol), citric acid monohydrate (74 mg, 0.34 equiv) in CH_2Cl_2 after purification by flash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **139c** (180 mg, 80%) as a colorless oil. ^{1}H NMR and ^{13}C NMR data were identical to literature report. HRMS (EI) calculated for $[C_{10}H_{13}BrO_2]^+$: 244.0099, found 244.0097.[137]



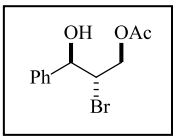
(1R*,2S*,3S*) 1-Phenyl-2-bromo-3-acetoxy butan-1-ol (174). 1-Phenyl-2-buten-1-ol was synthesized by using the literature procedure.[142] To the solution of crotonaldehyde (0.7 g, 10.0 mmol) in THF under argon was added phenyl magnesium chloride (9.2 mL, 1.2 M in Et_2O, 11.0 mmol) at 0 ^{o}C and the resulting solution was stirred for 2 hours. Reaction was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O (3 x 20.0 mL). The combined organic layer was washed with brine (20.0 mL), and water (20.0 mL). Organic layer was dried over anhydrous $MgSO_4$, filtered and solvent evaporation in rota vacuo gave 1-phenyl-2-buten-1-ol **173** (1.34 gm, 92 %) as a colorless oil which was used for the next step without purification.



Employing general procedure B and using **173** (148 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3 mg, 2 mol%), AcOH (60 mg, 1.0 mmol) in CH_2Cl_2 after purification by flash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **174** (244 mg, 85%) as a colorless oil: IR (neat) 3449 (br s), 3041 (s), 2980 (s), 2923 (s), 1741 (s), 1454 (s), 1374 (s), 1238 (s), 1046 (s), 701 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (d, J = 6.4 Hz, 3 H), 2.09 (s, 3H), 4.40 (t, J = 5.5 Hz, 1H), 4.81 (d, J = 5 Hz, 1H), 4.94 (dq, J = 12.4, 6.5 Hz, 1H), 7.33-7.42 (m, 5H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 21.1, 65.5, 70.3, 72.9,

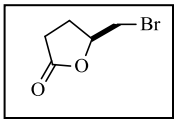
126.2, 128.4, 128.6, 139.8, 170.3; mass spectrum *m/z* (relative intensity) EI 288 (1.21, M^+), 286 (1.19, M^+), 207 (6), 149 (6), 148 (7), 147 (58), 120 (16), 107 (100), 105 (25), 91 (12), 79 (44), 77 (28), 61 (18).

(1S*,2S*) 1-Phenyl-2-bromo-3-acetoxy propan-1-ol (176). Employing literature procedure[142]



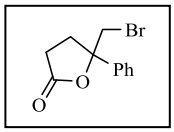
and using benzaldehyde (530 mg, 5.0 mmol) and vinyl magnesium bromide (5.5 mL, 1.0 M in THF) in THF gave pure 1-phenyl-2-propen-1-ol (**175,** 596 mg, 89%) which was used for next step without purification. Employing general procedure B and using 1-hydroxy-1-phenyl-2-propene **175** (134 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3 mg, 2 mol%), AcOH (60 mg, 1.0 mmol) in CH_2Cl_2 at room temperature after purification by flash chromatography (neutral alumina, 15-25% CH_2Cl_2 in petroleum ether, v/v) gave pure **176** (207 mg 76%) as a colorless oil: ^{1}H NMR and ^{13}C NMR data were identical to literature report.[143]

5-(Bromomethyl)-γ-butyrolactone (200). Employing general procedure B and using 4-pentenoic



acid (100 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (2 mol%) in CH_2Cl_2 at room temperature after purification by flash chromatography (neutral alumina, 25-35% CH_2Cl_2 in petroleum ether, v/v) gave pure compound **200** (170 mg, 95 %) as a colorless oil. ^{1}H NMR and ^{13}C NMR data were identical to literature report.[144]

5-Bromomethyl-5-phenyldihydrofuran-2-one (202). 4-Phenyl-4-pentenoic acid was prepared

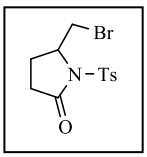


by the modification of literature procedure.[145] To the solution of methyl triphenyl phosphonium bromide (2.32 gm, 6.5 mmol) in THF under argon was added sodium *tert*-butoxide (1.25 gm, 13.0 mmol) at 0 ^{o}C and stirred for 30 minutes. Phenyl-4-oxo-pentanoic acid (890 mg, 5.0 mmol) was added and the resulting mixture was stirred

for 16 h. The solvent was evaporated in rota vacuo, treated with aqueous NaOH (10.0 mL, 1.0 M) and the aqueous layer was washed with CH_2Cl_2. The aqueous layer was treated with HCl (12.0M) until pH 2. The aqueous layer was then extracted with CH_2Cl_2 (3 x 10.0 mL), washed subsequently with brine (10.0 mL) and water (10.0 mL), dried over magnesium sulfate, filtered and solvent removal at rota vacuo gave **201** as a white solid which was used for the next step without purification.

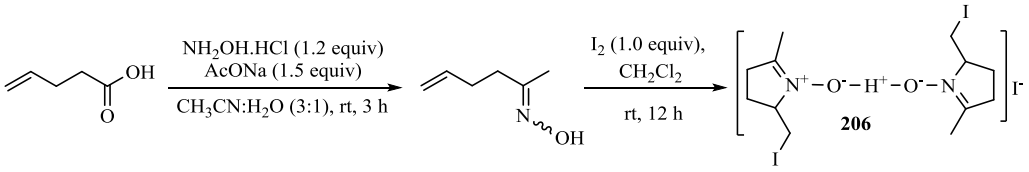
Employing general procedure B and using 4-phenyl-4-pentenoic acid **201** (176 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3 mg, 2 mol%), in CH_2Cl_2 at room temperature after purification by flash chromatography (neutral alumina, 25-35% CH_2Cl_2 in petroleum ether, v/v) gave pure **202** (243 mg, 95%) as a colorless oil. ^1H and ^{13}C NMR data are identical to literature report.[27]

5-(Bromomethyl)-1-tosylpyrrolidin-2-one (204). *N*-Tosyl 4-pentenamide was synthesized by using the slight modification of literature procedure.[146] To the solution of 4-pentenoic acid (0.5 g, 5.0 mmol) and *p*-tosylamine (0.85 gm, 5.0 mmol) in CH_2Cl_2 (20.0 mL) was added 1,3-dicyclohexylcarbodiimide (1.05 gm, 5.0 mmol) and 4-dimethylaminopyridine (56 mg, 0.5 mmol) at -20 ^oC and the resulting mixture was stirred for 12 hours with slowly warm up to room temperature. The removal of white solid by filtration followed solvent evaporation in rota vacuo followed by purification using flash column chromatography (silica, 20-30% EtOAc in petroleum ether) gave pure *N*-tosyl-4-pentenamide **203** (0.91gm, 72%) as a colorless oil. Employing general procedure B and using *N*-tosyl-4-pentenamide (182 mg, 1.0 mmol), NBS (178 mg, 1.0 mmol), DBU (3.0 mg, 2 mol%) and citric acid anhydride (74 mg, 0.33 mmol) in CH_2Cl_2 after purification by flash column chromatography

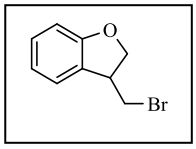


(silica, 20-30% EtOAc in petroleum ether) gave **204** (246 mg, 74 %) as a colorless solid. The identification of product was carried out on comparing their NMR spectra with literature one.[147]

Oximation of 4-pentenoic acid: 5-Hexen-2-one oxime was synthesized using 4-pentenoic acid (0.5 gm, 5.0 mmol), $NH_2OH.HCl$ (1.2 equiv) and AcONa (1.5 equiv) in acetonitrile and water (20.0 mL, $CH_3CN:H_2O$, 3:1) following literature procedure (0.47 gm, 83%).[148] Attempted cyclization of 5-hexen-2-one oxime in the absence of nitrogen or phosphorus catalyst employing literature procedure[148] gave **206** as a colorless solid.

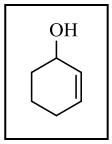


3-(Bromomethyl)-2,3-dihydrobenzofuran (208). Employing general procedure B and using



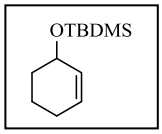
phenylvinyl ether **207** (134 mg, 1.0 mmol), *N*-bromosuccinimide (178 mg, 1.0 mmol), DBU (3.0 mg, 2 mol%), citric acid monohydrate (74 mg, 0.33equiv) in CH_2Cl_2 after purification by flash chromatography (neutral alumina, 25-35% CH_2Cl_2 in petroleum ether, v/v) gave pure **208** (166 mg, 78%) as a colorless soild.^{1}H NMR and ^{13}C NMR data were identical to literature report.[114]

1-Cyclohexenol (195a). The reduction of cyclohexenone to 2-cyclohexenol was carried out with



lithium aluminium hydride using literature procedure.[149] The ^{1}H and ^{13}C NMR data of the compound was similar to the literature report. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54-1.64 (m, 2H), 1.67-1.77 (m, 1H), 1.83-1.90 (m, 1H), 1.96 (s, 1H), 2.02-2.06 (2H), 4.19 (s, 1H), 5.73-5.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 25.0, 31.9, 65.4, 129.8, 130.5.

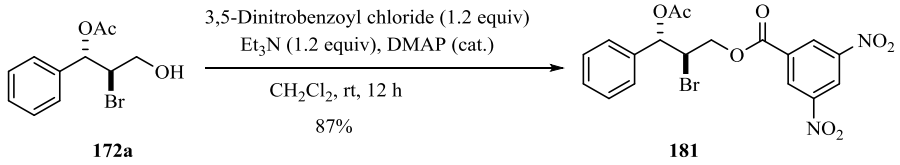
***tert*-Butyldimethyl silyl protected 2-cyclohexenol (195b).** The protection of 2-cyclohexenol was



carried out using literature procedure.[150] To the solution of 2-cyclohexenol (1.1 gm, 11.2 mmol) in CH_2Cl_2 (40.0 mL) was added Et_3N (2.26 gm, 22.4 mmol), imidazole (1.52 g, 22.4 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP, 20 mg) at 0 ^oC. Next the solution of $^tBuMe_2SiCl$ in CH_2Cl_2 (15.0 mL) was added dropwise over 30 min. The reaction mixture was gradually warmed to room temperature over 12 hours with continous stirring, diluted with water (15.0 mL), extracted with CH_2Cl_2 (3 x 15.0 mL). The combined organic layer was washed subsequently with water (15.0 mL), brine (15.0 mL), dried over anhydrous $MgSO_4$, filtered and concerntrated in rota vacuo. The purification of product by flash column chromatography (neutral silica, 5-10% Et_2O in petroleum ether, v/v) gave **195b** (2.11 gm, 89%) as colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.88 (s, 6H), 1.51-1.61 (m, 2H), 1.74-1.87 (m, 2H), 1.91-2.05 (m, 2H), 4.25 (s, 1H), 5.63-5.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.6 (2-carbons), -3.0, 19.7, 24.9, 32.5, 66.7, 129.0, 131.2.

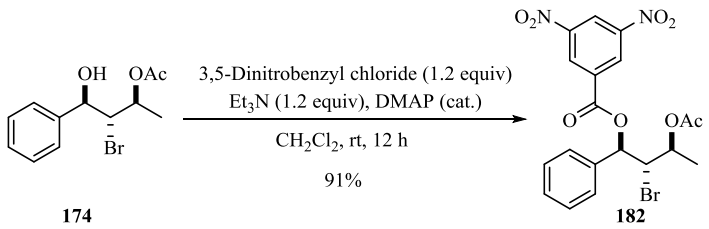
General Procedure C: Syntheses of 3,5-dinitrobenzoyl derivatives of alcohol. The 3,5-dinitrobenzoyl derivatives of alcohol were prepared using the modification of literature procedure.[151] To the solution of starting alcohol (1.0 equiv) in anhydrous CH_2Cl_2 was added 3,5-dinitrobenzoyl chloride (1.2 equiv), Et_3N (1.2 equiv) and catalytic amounts of 4-*N*,*N*-dimethylaminopyridine (DMAP) under argon and the resulting mixture was stirred for 12 hours at room temperature. The reaction mixture was quenched with water, extracted with CH_2Cl_2 (3 times). The combined organic phase was washed five times with water and once with saturated brine solution, dried over anhydrous $MgSO_4$, filtered and removal of solvent in rota vacuo. The purification of product using flash column chromatography (silica, 10-20% EtOAc in petroleum ether, v/v) gave 3,5-dinibrobenzoyl derivatives as a pale yellow solid.

(2R*,3R*) 2-Bromo-1-(3,5-dinitrobenzyol)-3-phenyl-3-acetoxy-propanol (181). Employing general procedure C and using **172a** (136 mg, 0.5 mmol) 3,5-dinitrobenzoyl chloride (138 mg, 0.6 mmol), Et_3N (61 mg, 0.6 mmol), DMAP (5 mg) in dry CH_2Cl_2 (5.0 mL) at room temperature after flash column chromatography (silica, 10-20% EtOAc in petroleum ether, v/v) gave pure **172a** (203 mg, 87%) as a pale yellow solid: m.p. 107.2-109.7 ^oC, IR (neat) 3099 (s), 2917 (s), 2832 (s), 1733 (s), 1726 (s), 1541 (s), 1357 (s), 1267 (s), 1157 (s), 1071 (s), 719 (s), 699 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (s, 3H), 4.67 (dt, J = 10.6, 5.1 Hz, 1H), 4.72-4.82 (m, 2H), 6.20 (d, J = 5.5 Hz, 1H), 7.26-7.41 (m, 5H), 9.05 (d, J = 1.9 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 50.3, 65.8, 75.0, 112.7, 126.7, 128.7, 128.8, 129.4, 132.9, 136.3, 148.6, 161.8, 169.3.



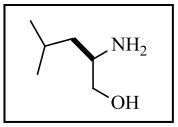
172a **181**

(1S*,2S*,3S*) 1-(3,5-Dinitrobenzyol)-1-phenyl-2-bromo-3-acetoxy-1-butanol (182). Employing general procedure C and using **174** (144 mg, 0.5 mmol) 3,5-dinitrobenzoyl chloride (138 mg, 0.6 mmol), Et_3N (61 mg, 0.6 mmol), DMAP (5 mg) in dried CH_2Cl_2 (5.0 mL) at room temperature after flash column chromatography (silica, 10-20% EtOAc in petroleum ether, v/v) gave pure **182** (218 mg, 87%) as a pale yellow solid: m.p. 111.4-114.2 ^oC; IR (neat) 3100 (s), 2920 (s), 1739 (s), 1733 (s), 1546 (s), 1346 (s), 1273 (s), 1161 (s), 1073 (s), 721 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (d, J = 6.5 Hz, 3H), 2.08 (s, 3H), 4.66 (t, J = 6.4 Hz, 1H), 4.88 (dt, J = 12.0, 6.0, 1H), 6.29 (d, J = 6.5 Hz, 1H), 7.41-7.49 (m, 5H), 9.20-9.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2, 21.0, 58.9, 122.7, 127.0, 128.9, 129.0, 129.6, 129.7 (2-carbon), 133.3, 135.6, 148.7, 161.3, 170.0.

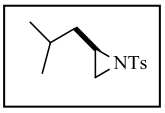


174 **182**

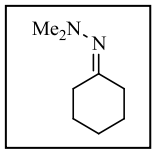
L-Leucinol (209). The title compound was synthesized from L-leucine using literature procedure[152] in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (dd, J = 11.5, 6.4 Hz, 6H), 1.17 (t, J = 7.4 Hz, 1H), 1.52 (m, 1H), 1.57-1.64 (m, 1H), 2.91-2.97 (m, 1H), 3.26 (dd, J = 11.0 Hz, 8.3 Hz, 1H), 3.55 (dd, J = 11.0, 3.2 Hz, 1H), 3.69 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 23.9, 24.5, 42.2, 50.7, 65.5.



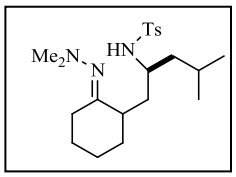
(*S*) *N*-(*p*-Toluenesulfonyl)-2-(2-methylpropyl)-aziridine (212). Compound **212** was synthesized by using the literature procedure.[117] To the solution of L-leucinol (1.17 gm, 10.0 mmol) in CH_2Cl_2 (20.0 mL) was added Et_3N (4.2 mL, 30.0 mmol), TsCl (4.76 gm, 25.0 mmol) and DMAP (50 mg) under argon at 0 ^{o}C and the resulting reaction mixture was stirred for 24 hrs with slowly warming to room temperature. The reaction was quenched with saturated NH_4Cl solution (10.0 mL), diluted with water (20.0 mL) and extracted with CH_2Cl_2 (3 x 20.0 mL). The combined organic layer was washed subsequently with brine (20.0 mL) and water (20.0 mL), dried over anhydrous $MgSO_4$, filtered and solvent was evaporated in the rota vacuo. The purification of product using flash column chromatography (silica, 10-20% Et_2O in petroleum ether, v/v) gave pure **212** (2.18 gm, 86%) as white crystal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (dd, J = 6.9, 2.8 Hz, 6H), 1.23-1.29 (m, 2H), 1.49-1.58 (m, 1H), 1.94 (d, J = 4.6 Hz, 1H), 2.35 (s, 3H), 2.54 (d, J = 6.9 Hz, 1H), 2.67-2.73 (m, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 21.9, 26.7, 34.0, 39.0, 40.3, 127.9, 129.6, 135.1, 144.4.



***N,N*-Dimethyl cyclohexylhydrazine (214).** Compound **214** was prepared by using a slight modification of literature procedure.[153] To the solution of cyclohexanone (1.96 gm, 20.0 mmol) in EtOH (40.0 mL) was added dimethylhydrazine (1.34 gm, 22.0 mmol) and the resulting mixture was reflux for 4 hrs. The solvent was evaporated in rota vacuo, crude product was diluted with H_2O (20.0 mL), extracted with Et_2O (3 x 20.0 mL), combined organic layer was washed with saturated aqueous NH_4Cl, dried over anhydrous $MgSO_4$, filtered and solvent evaporation gave **214** which was used for next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (br s, 4H), 1.64 (br s, 2H), 2.16-2.19 (m, 2H), 2.37 (s, 6H), 2.44 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 26.4, 27.3, 28.4, 35.8, 47.4, 169.9.

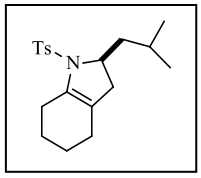


2-(2-(*p*-Toluenesulfonylamino)-4-methylpenthyl)-*N,N*-dimethylcyclohexylhydrazine (215).[154] The synthesis of **215** was carried out using slight modification of literature procedure. To the freshly prepared LDA (2.2 mmol) in THF under argon was added **214** (280 mg in 3.0 mL THF, 2.0 mmol) at 0 ^{o}C and the resulting solution was stirred for 6 hrs. Next, *N*-tosylazirdine **212** (506 mg in 2.0 mL THF, 2.0 mmol) was added at 0 ^{o}C and the resulting solution was stirred for 12 hours with slightly warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (5.0 mL), diluted with water (5.0 mL) and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layer was washed subsequently with brine (10.0 mL), water (10.0 mL) and dried over anhydrous $MgSO_4$. The removal of solvent in rota vacuo followed by purification of product using flash column chromatography (silica, 60-90% Et_2O in petroleum ether, v/v) gave pure **215** as colorless oil (0.59 gm, 76%).^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H), 1.03-1.80 (m, 16H), 2.23-2.29 (m, 1H), 2.49 (s, 6H), 3.10 (dt, J = 12.8, 3.2 Hz, 1H), 3.29-3.35 (m,



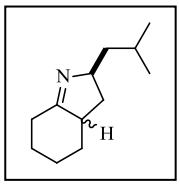
1H), 7.27 (d, J = 7.8 Hz, 2H), 7.75 (J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.3, 22.9, 24.5, 25.4, 26.9, 28.5, 35.1, 36.0, 41.2, 44.9, 47.7, 50.1, 127.2, 129.4, 138.5, 142.6, 172.3.

***N*-(*p*-Toluenesulfonyl)-2,3,4,5,6,7-hexahydro-2-(2-methylpropyl)-1H-indole (216).** The



cleavage of hydrazone was carried out using literature procedure.[155] To the solution of **215** (394 mg, 1.0 mmol) in Et_2O (5.0 mL) was added saturated aqueous solution of oxalic acid (2.0 mL) and the resulting solution was stirred for 18 hrs at room temperature. The reaction mixture was neutralized using saturated aqueous $NaHCO_3$, extracted with Et_2O (3 x 5.0 mL), combined organic layer was washed with brine (5.0 mL), water (5.0 mL), dried over anhydrous $MgSO_4$, filtered and solvent evaporated in rota vacuo gave **216** as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 6.5 Hz, 2H), 1.27-1.32 (m, 1H), 1.47-1.70 (m, 4H), 1.75-1.85 (m, 2H), 1.90-1.97 (m, 1H), 2.03-2.08 (m, 1H), 2.29-2.34 (m, 1H), 2.43 (s, 3H), 2.52-2.60 (m, 1H), 3.92-3.97 (m, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.4, 22.5, 22.9, 23.0, 24.2, 25.1, 25.5, 37.8, 46.2, 59.5, 124.2, 127.3, 129.3, 134.1, 134.9, 143.1.

2-(2-Methylpropyl)-3,3a,4,5,6,7-hexahydro-2H-indole (217). The cleavage of *N*-tosyl group



was carried out by slight modification of literature procedure.[118] To the solution of **216** (333 mg, 1.0 mmol) in MeOH (5.0 mL) was added magnesium turnings (480 mg, 20.0 mmol) and the resulting mixture was reflux for five hours. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, filtered, solvent was evaporated in rota vacuo gave **217** (141 mg, 79%, dr 3:1) as a colorless oil. Refluxing the mixture of **216** (83 mg, 0.25 mmol) with phenol (47 mg, 0.5 mmol) in 48% HBr (3.0 mL) using literature procedure[119] gave **217** (30 mg, 67%, dr 3:1) as colorless oil. **Major:** ^{1}H NMR (500 MHz, $CDCl_3$)

δ 0.96 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H), 1.24-1.32 (m, 2H), 1.41-1.48 (m, 2H), 1.68-1.88 (m, 4H), 1.97-2.01 (m, 2H), 2.10-2.17 (m, 2H), 2.62-2.67 (m, 2H), 3.73 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 23.0, 25.2, 25.8, 26.5, 31.8, 34.9, 37.4, 47.1, 48.2, 68.9, 178.1 **Minor:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H), 1.09-1.15 (m, 2H), 2.44-2.57 (m, 2H), 2.53-2.57 (m, 4H), 4.08 (br s, 1H), rest of the hydrogens were imbedded under major isomer hence cannot identified; ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 22.9, 25.4, 25.7, 27.1, 32.0, 34.8, 35.4, 35.5, 46.1, 47.4, 178.2; mass spectrum *m/z* (relative intensity) EI 179 (9.71, M^+), 164 (13), 136 (89), 123 (96), 122 (100), 109 (18), 94 (64), 80 (37), 67 (31), 55 (14).

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CHAPTER IV

CONJUGATE ADDITION REACTIONS OF GRIGNARD REAGENTS TO 4H-PYRIDONES

4.1 Introduction

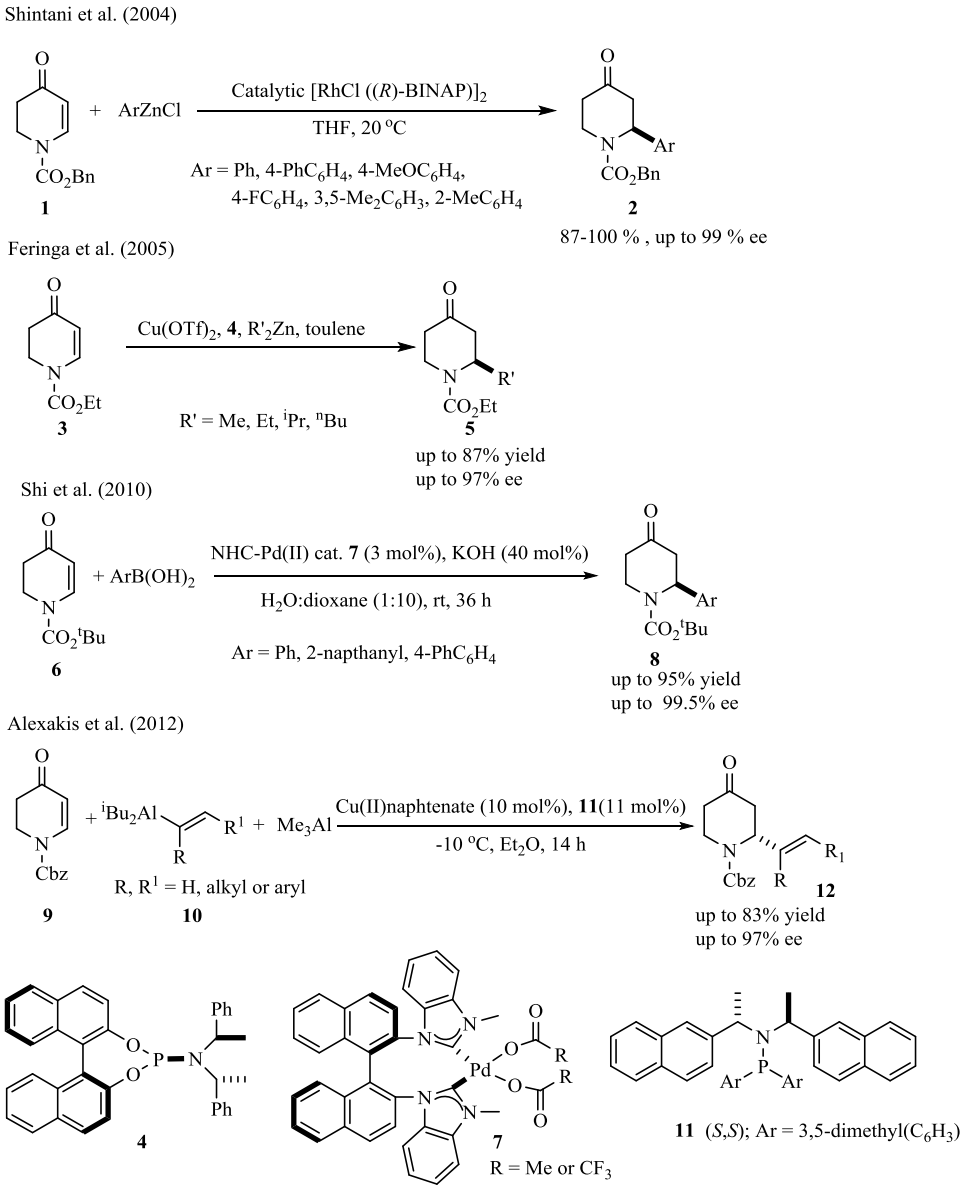
Alkaloids are most ubiquitous nitrogen bearing compounds and are building blocks of several natural products and synthetic intermediates.[1] These compounds are used as narcotics, poisons, stimulants and medicine for several years.[1-3] Nature has ample examples bearing profusion of multi-cyclic system with bridgehead nitrogen atom. Both simple and annulated piperidines [e.g., indolizidines (1-azabicyclo [4.3.0] nonanes) and quinolizidines (1-azabicyclo [4.4.0] decanes)], and 12000 other piperidine derivatives are in clinical trials[4] over a ten year period. Due to their high biological activity, significantly large interests for the total synthesis of piperidine analogues are devoted in recent years. Although, varieties of piperidine alkaloids are isolated from natural products, the total syntheses of only a few of them are reported in the literature. Numerous asymmetric routes for the synthesis of piperidine moiety of natural products are reported[5, 6] which are generally based on four strategic approaches[2]: i.) intramolecular S_N2 substitution reactions of an activated acyclic precursor bearing pre-established stereogenic centers; ii.) α-functionalization of an existing six-membered nitrogen heterocycle there by generating stereogenic centers; iii.) ring enlargement of prolinols and pyrolidine derivatives and iv.) ring closing metathesis on dialkyl substituted nitrogen derivatives where each alkyl group contains an appropriately positioned alkene functional group. While each of the above strategies rely on manipulation of the chiral pool for appropriate starting materials or use of chiral auxiliaries,[5-7] these protocols are effective for the synthesis of a wide variety of *N*-heterocycles.

4.2 Pioneer Study

4.21 Conjugate Addition on 2,3-Dihydro-4-pyridone

The conjugate addition of organometallic reagents to 2,3-dihydro-4-pyridones is one of the most common method for the synthesis of 2-substituted piperidones. An extensive search of chemical literature showed numerous methodologies for the diastereo- and enantioselective synthesis of substituted piperidines via piperidones and many of the products are in clinical and preclinical trials.[4] All of these methodologies are focused on developing versatile and stereocontrolled routes for the synthesis of piperidinone derivatives.[8-11] Most of these methods rely on using stoichiometric amounts of chiral reagents along with few catalytic routes for the synthesis of 2-substituted 4-piperidinones. Among the established method, rhodium and copper catalyzed conjugate addition of organometallic reagents to 2,3-dihydropyridone dominated the literature. Shintani and coworkers reported the first enantioselective route for the conjugate addition of arylzinc chloride to 2,3-dihydropyridone **1** promoted by chiral rhodium catalyst.[8] Although, the reaction of $PhB(OH)_2$ with 2,3-dihydropyridone **1** in the presence of catalytic amounts of $Rh(acac)(C_2H_4)_2$-*(R)*-BINAP gave 1,4-adduct, the yield was poor (33%). On the other hand, the use of electronically and sterically diverse arylzinc reagents (electron rich and electron deficient aryl group) under identical conditions gave conjugate addition product **2** in excellent yields and excellent enantioselectivity (up to 100% yield and up to 99.5 ee).

Scheme 4.1 Enantioselective 1,4-Addition to 2,3-Dihydropyridones.[8-13]



Feringa and coworkers used copper catalysis for the conjugate addition reaction of dialkylzinc to 2,3-dihydropyridone **3** in the presence of homochiral phosphoramidite catalyst **4**. The best enantioselectivity was observed while using toluene as a solvent.[9] Both diethylzinc and diisopropylzinc gave good yields of 1,4-adduct at -25 °C while higher temperature (0 °C) was

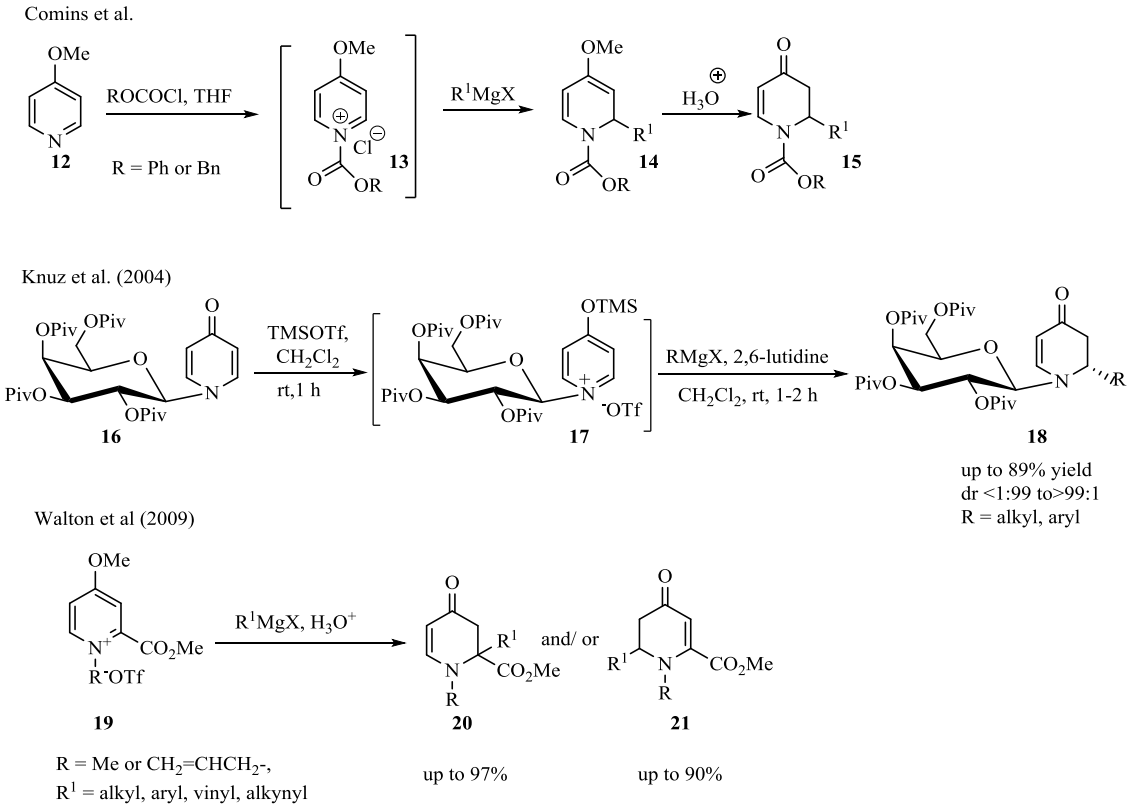
needed for dimethylzinc for completion of reaction displaying the less reactive nature of the zinc reagents. Despites these results, dibutylzinc gave poor yield and poor enantioselectivity under identical conditions and authors failed to rationalize the low enantioselective process. Shi and coworkers[12] reported the bidentate *bis*-(*N*-heterocyclic carbene)-palladium(II) (**7**) catalyzed enantioselective 1,4-conjugate addition of arylboronic acids to 2,3-dihydro-4-pyridone **6** in the presence of potassium hydroxide in mixed solvent system (i.e.; H_2O:1,4-dixoane, 1:10). The reaction gave 1,4-adduct **8** in excellent yield and excellent enantioselectivity (up to 96%, <95.5% ee). Recently, Alexakis and Mùller reported the copper based bifunctional phosphine-amine **11** catalyzed conjugate addition reaction of vinyl alanes **10** to 2,3-dihydro-4-pyridone **9**.[13] The co-activation of the vinyl alanes using catalytic amounts of Me_3Al as Lewis acid in diethyl ether was essential for obtaining optimum yields and enantioselectivity. The newly develop method provided opportunity for transferring vinyl group where previous attempt failed.[8, 12] In addition to these methodologies, enantioselective 1,4-conjugate addition reactions of arylboroxines,[11] aryl-(2-(hydroxymethyl)-phenyl)-dimethylsilanes,[14] arylsiloxanes[15] and alkyl aluminum reagents[16] to 2,3-dihydro-4-pyridones were also reported in the literature.

4.22 1,2-Addition on Pyridinium Salts

Pyridinium salts are highly attractive synthetic precursor for the synthesis of substituted piperidine ring present in the complex organic molecule upon reactions with organometallic reagents. The 1,2-addition reaction of Grignard reagents to pyridinium salts have been proven valuable method for the synthesis of substituted piperidinone moiety present in the synthetic targets.[5, 6, 17-20] Comin and coworkers enormously expanded the field of enantioselective 1,4-conjugate addition of organometallic reagents to pyridinium salts employing chiral auxiliary in

the last three decades.[6, 9, 17, 18, 20-23] Kunz and coworkers[24] reported the diastereoselective 1,4-conjugate addition of organolithium, organomagnesium and organocopper reagents to pyridinium salt generated in situ from the reaction of *N*-galactosyl-4-pyridone **16** with TMSOTf. The reaction gave good yield of 1,4-adduct under optimized reaction conditions. Control experiment involving the reaction of *N*-galactosyl-4-pyridone **16** with organometallic reagents in the absence of TMSOTf failed confirming the necessity of additives for the reaction. Recently, Donohoe and coworkers[19] reported the 1,2-addition reaction of Grignard reagents to pyridinium salt **19** which on acid hydrolysis gave 2-substituted 2,3-dihydropyridone derivatives. Interestingly preferred nucleophilic attack of alkyl Grignard reagents (e.g., Me, Et, ^{n}Hex or ^{t}Bu) at C-2 of *N*-methyl protected pyridinium salts gave product **20** while the application of vinyl and allyl Grignard reagents gave C-6 addition product **21**. The author claimed that the harder nucleophile (i.e., Me, Et, ^{n}Hex or ^{t}Bu Grignard reagents) preferred the attack at harder C-2 center while the C-6 attack was the preferred process for the softer nucleophile (vinyl and allyl Grignard reagents). Similarly, *N*-allyl pyridinium salt furnished exclusive C-2 addition product on reaction with alkyl Grignard reagents but the application of aryl or vinyl Grignard reagent under identical reaction condition gave the mixture of C-2 and C-6 adduct. Although, the detailed mechanistic rationalization for the poor regioselectivity was not proposed, the author initially claimed that the *N*-allyl group force the pyridinium salt in a conformation that hindered the C-6 addition of aryl or vinyl Grignard reagents and reduce the nucleophilic attack at that center. However, phenyl and vinyl Grignard reagents in the presence of stoichiometric amounts of $ZnCl_2$ gave exclusive C6 addition product.

Scheme 4.2 1,2-Addition Reactions of Grignard Reagents to Pyridinium Salt.[6, 9, 19-23]



4.23 Conjugate Addition on 4-Pyridone

N-Carbomyl-4-pyridones are highly versatile synthetic intermediates for the synthesis of substituted piperidine ring presents in several natural products. These substrates can be easily synthesized and have high stability toward air and moisture. The rich functionality of the molecule provides opportunity for the synthesis of different products upon reaction with different organometallic reagents (**Figure 4.1**). Catalytic asymmetric conjugate addition to 4-pyridone offers absolute stereochemistry, while tandem or subsequent transformations on functional group controlled 6-membered ring conformations. Carbonyl and enolate chemistry offer opportunities

for the synthesis of substituted heterocycles initially formed. However promoting a reaction in a particular site in stereocontrolled fashion is still a highly daunting challenge for synthetic organic chemist.

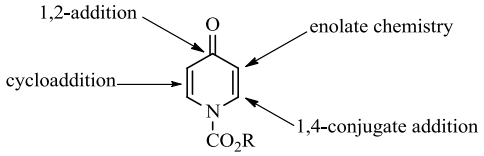
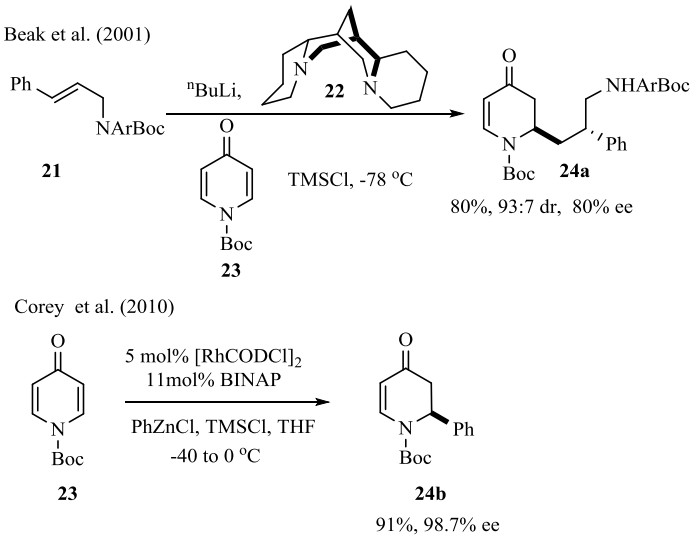


Figure 4.1 Highly Versatile *N*-Carbomyl-4-pyridone with Possible Reaction Sites.

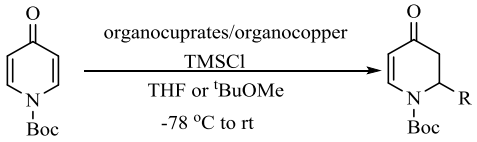
The 1,4-conjugate addition of organometallic reagents to Michael substrate is one of the common reactions in organic synthesis. Among the various kinds of Michael acceptors, *N*-carbomyl-4-pyridones are highly versatile substrates and are building blocks for the synthesis of piperidine ring present in large numbers of natural products. Most of the methods reported rely on copper catalysis for conjugate addition reactions. Although, 1,2-addition of organometallic reagents to *N*-carbomyl-4-methoxypyridinium salts also give 2-substitued-*N*-carbomoyl pyridone (*vide supra*),[6, 17, 18, 20, 21] the addition of organometallic reagents to *N*-carbomyl-4-pyridones offer more opportunities for controlling the stereochemistry in the piperidine ring. In 2001, Beak and coworkers[1] reported the enantioselective 1,4-addition reaction of organolithium reagents to *N*-Boc-4H-pyridone **23** catalyzed by sparteine **22**. This method gave 1,4-addition product in high yields, diastereo- and enantioselectivity but required trimethylsilylchloride (TMSCl) additives. Corey and coworkers[25] employed RhCl(*S*)-BINAP catalyst for the enantioselective 1,4-conjugate addition of arylzinc chloride to *N*-Boc-4H-pyridone in the presence of TMSCl affording **24b** in excellent yields and excellent enantioselectivity (91%, 98.7% ee).

Scheme 4.3 Enantioselective 1,4-Conjugate Addition of Organometallic Reagents to *N*-Boc-4H-pyridone.[1,25]



1,4-Conjugate addition of Gilman and alkyl/arylcyanocuprate reagents to *N*-Boc-4H pyridone **23** using TMSCl (3.0 equiv) as an additives was investigated in our laboratory.[26] The control experiment confirmed that conjugate addition was failed in the absence of TMSCl. Me, Et, ^{n}Bu, ^{s}Bu, ^{t}Bu and Ph groups were successfully transferred in conjugate fashion when corresponding organocopper/cuprate reagents were employed for reaction affording moderate to good yields of 1,4-adduct (**Table 4.1**). A slightly higher yield was observed with Gillman's reagents in comparison to corresponding monoalkyl copper reagents reflecting the facility of ligand transfer and *N*-Boc-pyridone reactivity. It was purposed that the reactions was promoted via 1,4-conjugate addition pathway to pyridone-TMSCl complex rather than 1,2-addition to pyridinium salts.

Table 4.1 1,4-Addition of Organocuprate Reagents to *N*-Boc-4H-Pyridone.[26, 27]



23 **25**

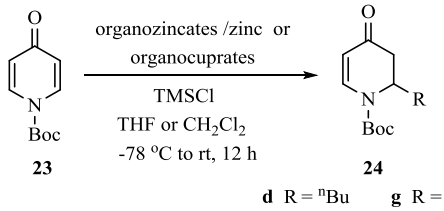
c R = Me **d** R = ^{n}Bu
e R = ^{s}Bu **f** R = ^{t}Bu
b R = Ph

entry	reagents[a]	product	% yields[b]
1	Me_2CuLi	**24c**	69
2	MeCuCNLi	**24c**	83-85
3	$^{n}Bu_2CuLi$	**24d**	77-80
4	$^{s}Bu_2CuLi$	**24e**	78
5	^{s}BuCuCNLi	**24e**	59-65
6	$^{t}Bu_2CuLi$	**24f**	59-65
7	^{t}BuCuCNLi	**24f**	65
8	Ph_2CuLi	**24b**	80-85
9	PhCuCNLi	**24b**	81

[a] Organocuprate reagents were prepared by the reaction of RLi (2.0 equiv) with CuCN.2LiCl. TMSCl (3.0 equiv) was employed for the reactions. [b] Yields are based on isolated products purified by flash column chromatography.

Conjugate addition of the organozinc and organozincate reagents to 4-pyridone in the presence or absence of copper catalyst using TMSCl as additives was also investigated in our laboratory. Lithium tri-*n*-butylzincates gave moderate yield of 1,4-adduct in the absence of CuCN (**Table 4.2**, entry 1). Although, attempted tandem conjugate addition-α-allylation reactions by the addition of allyl bromide after the completion of conjugate addition failed, the reaction offered higher yield of the 1,4-adduct (entry 2). Mixed organozincate, monoalkylzinc halide and dialkylzinc reagents all underwent 1,4-conjugate addition to *N*-Boc-4H-pyridone in the presence of stoichiometric or catalytic amounts of CuCN using TMSCl as an additives with moderate to good yields (entries 3-6).

Table 4.2 1,4-Addition of Mix Organocopper/Zinc Reagents to *N*-Boc-4H-Pyridone.[26,27]

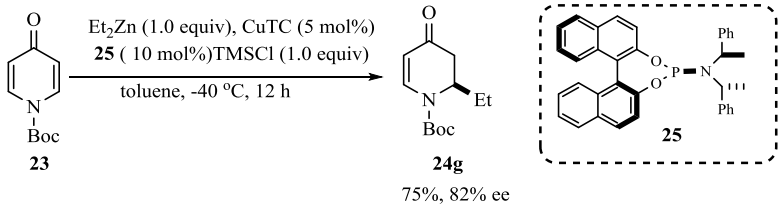


entry	reagents[a]	%CuCN	R	product	% yields[b]
1	$^{n}Bu_3ZnLi$	-	^{n}Bu	**24d**	63
2	$^{n}Bu_3ZnLi$	0.1[c]	^{n}Bu	**24d**	83
3	$^{n}Bu^{t}Bu_2ZnLi$	1.0	^{n}Bu	**24d**	40
4	$^{n}BuZnBr$	1.0	^{n}Bu	**24d**	70
5	Et_2Zn	1.0[d]	Et	**24g**	77
6	Et_2Zn	0.1[d]	Et	**24g**	62

[a] Organozinc/organozincate reagents were prepared from the reaction of RLi with $ZnBr_2$ in the presence or absence of CuCN unless otherwise noted. TMSCl (3.0 equiv) was employed for the reactions. [b] Yields are based on isolated products purified by flash column chromatography. [c] Reaction was carried out in the presence of allyl bromide (1.0 equiv). [d] CuCN.2LiCl was used for the reaction.

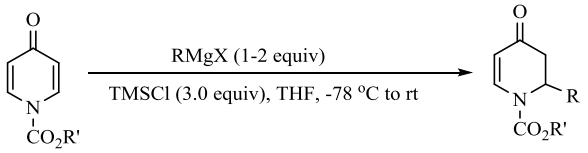
Interestingly copper 2-thienylcarboxylate (CuTC) and chiral phosphoramidite **25** catalyze conjugate addition of diethylzinc to *N*-Boc-4H-pyridone in the presence of TMSCl gave 1,4-adduct **24g** in good yield and good enantioselectivity (**Scheme 4.4**). This result confirmed that TMSCl did not disrupt the Zn-Cu complex and was involved for the selectivity on coordinating with binapthol based catalyst and accelerated the conjugate addition reaction.

Scheme 4.4 Enantioselective 1,4-Addition of Diethylzinc to *N*-Boc-4H pyridone.[26]



1,4-Addition reactions of Grignard reagents to *N*-carbomyl-4H-pyridone **23** in the presence or absence of CuCN using TMSCl (3.0 equiv) was investigated in our laboratory.[26, 27] The reaction of ^{n}BuMgCl with *N*-Boc-4H-pyridone in the presence of 10 mol% CuCN and TMSCl (3.0 equiv) gave 1,4-adduct in good yields (**Table 4.3**, entry 1). Surprisingly, yield of 1,4-adduct was enhanced when CuCN was reduced to 1 mol % (entry 2) and further higher yield was achieved in the absence of CuCN (entry 3). In these reactions, not a trace amounts of 1,2-adduct was observed. The control experiment in the absence of both CuCN and TMSCl gave only a trace amounts of 1,4 adduct (entry 4). ^{n}BuMgCl underwent 1,4-conjugate addition reactions to *N*-ethoxycarbamoyl-4H-pyridone **25** but with slightly lower yields (entry 5). ^{i}PrMgCl also underwent 1,4-conjugate addition reactions to **25** but with moderate yields. Besides, 2-$MeOC_6H_4MgI$ and 2-MeC_6H_4MgBr gave better yield of 1,4-adduct in the presence of catalytic amounts of CuCN (entries 7 and 9 respectively) than in the absence of CuCN catalyst for 2-$MeOC_6H_4MgI$ (entry 8). Not surprisingly, the heteroaryl Grignard reagents like 2-thienyl and 2-furyl Grignard reagents underwent 1,4-conjugate addition reactions in the absence of Cu(I) salts but in the presence of TMSCl (3.0 equiv) as an additives in good yields (entries 10 and 11). The low yields of 1,4-adducts while running reaction of Grignard reagents with *N*-ethoxycarbamoyl-4H-pyridone **25** prompted to use *N*-Boc-4H-pyridone for further studies.

Table 4.3 Conjugate Addition of Grignard Reagents to *N*-Carbamoyl-4H-Pyridone. [27,28]



23 R' = ^{t}Bu
25 R' = Et

24 R' = ^{t}Bu
26 R' = Et

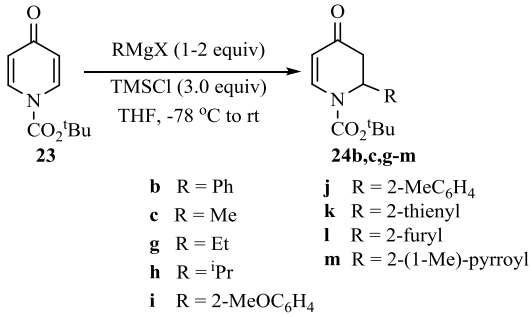
b R = Ph
d R = ^{n}Bu
h R = ^{i}Pr
i R = 2-MeOC$_6$H$_4$
j R = 2-MeC$_6$H$_4$
k R = 2-thienyl
l R = 2-furyl

entry	SM	R (equiv)	CuCN (mol%)[a,b]	product	% yield [c]
1	**23**	^{n}Bu (1.1)	10	**24d**	79
2	**23**	^{n}Bu (1.1)	1	**24d**	85
3	**23**	^{n}Bu (1.1)	0	**24d**	90
4	**23**	^{n}Bu (1.1)	0	**24d**	<5[d]
5	**25**	^{n}Bu (1.1)	10	**26d**	76
6	**25**	^{i}Pr (1.2)	0	**26h**	60
7	**25**	2-MeOC$_6$H$_4$ (1.2)	10	**26i**	71
8	**25**	2-MeOC$_6$H$_4$ (1.2)	0	**26i**	46
9	**25**	2-MeC$_6$H$_4$ (1.2)	10	**26j**	72
10	**25**	2-thienyl (2.0)	0	**26k**	78
11	**25**	2-furyl (2.0)	0	**26l**	75

[a] All reactions were run in THF using 1.1-2.0 equiv of R^{1}MgX (X = Cl, Br). TMSCl (3.0 equiv) was added as an additive. 4-Pyridone (**23** or **25**) was added at -78 °C and allowed to warm to room temperature over 12 hrs. [b] CuCN was added to a flask charged with argon as a solid and dry THF was added followed by addition of R^{1}MgCl at -78 °C. [c] Yields are based on isolated product purified by column chromatography. [d] No TMSCl was added.

Simple commercially available Grignard reagents such as methyl-, ethyl- and isopropyl magnesium halide as well as more complex in situ generated Grignard reagents such as 2-thienyl magnesium bromide, 2-furyl magnesium bromide, 2-MeC$_6$H$_4$MgBr, 2-MeOC$_6$H$_4$MgBr and 2-(1-methyl)-pyrrolyl magnesium bromide were successfully transferred to *N*-Boc-4H-pyridone **23** on 1,4-conjugate fashion with moderate to excellent yield (**Table 4.4**, entries 1-10). However, the feasibility of the transfer of more complex Grignard reagents and subsequent second conjugate addition reaction was not completed by my senior which was in fact the starting point of my research in this project.

Table 4.4 1,4-Addition of Grignard Reagents to *N*-Boc-4H-Pyridone using TMSCl as Additives. [27,28]



entry	R (equiv.)[a]	product	% yields[b]
1	Me (1.2)	**24c**	40
2	Et (1.2)	**24g**	89
3	Et (1.2)	**24g**	83[c]
4	^{i}Pr (1.2)	**24h**	86
5	Ph (1.1)	**24b**	85
6	2-MeOC$_6$H$_4$ (1.2)	**24i**	86
7	2-MeC$_6$H$_4$ (1.2)	**24j**	95
8	2- thienyl (2.0)	**24k**	83
9	2- furyl (2.0)	**24l**	85
10	2-(1-methyl)-pyrrolyl (1.2)	**24m**	70

[a] All reactions were run in THF using 1.1-2.0 equiv of RMgX (X = Cl, Br). TMSCl (3.0 equiv) was added as an additive. *N*-Boc-4H-pyridone was added at -78 °C and allowed to warm to room temperature over 12 hrs. [b] Yields are based on isolated product purified by column chromatography. [c] Reaction was run in a 1:1 mixture of THF and ^{t}BuOMe.

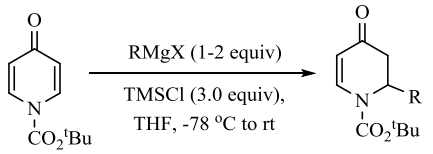
Hence the main objective of the project reported in this chapter was the development of general and divergent strategies for the conjugate addition of Grignard reagents to 4H-pyridone using TMSCl or $BF_3.OEt_2$ as additives. The optimized reaction conditions discovered for the first conjugate addition reaction was next employed for the stereoselective 1,4-conjugate addition of Grignard reagents to 2-substituted 2,3-dihydropyridones **24**. A part of this result was recently published and reprinted with the permission from American Chemical Society.[28]

4.3 Results

4.31 Conjugate Addition to *N*-Carbomoyl-4H-Pyridone

As a continuation of previous work in our laboratory, the scope of functionalized Grignard reagents for the 1,4-conjugate addition reaction to *N*-Boc-4-pyridone using TMSCl as additives was further investigated. The reaction of benzylmagnesium bromide and 1-napthylmagnesium bromide with *N*-Boc-4H-pyridone in the presence of TMSCl (3.0 equiv) as additives gave 1,4-adduct in good yields (**Table 4.5**, entries 1 and 2, 81% and 79% respectively). Functionalized aryl Grignard reagents like 4-$Me_2NC_6H_4MgBr$, 5-(1-methyl)-indolylMgI, 2-$ClCH_2C_6H_4MgI$ all underwent 1,4-conjugate addition in good yields (entries 3-5). The application of vinyl Grignard reagents under optimized reaction conditions also gave high yields of 1,4-adduct (entries 6 and 7). However attempted transfer of 2-$NO_2C_6H_4$-, 2-(1-methyl)-imidazoyl-, 2-pyridinyl and 1,3-dimethyl-5-uracelyl group failed under optimized reaction conditions (entries 8-11). Besides, attempted addition of lithium enolate derived from acetophenone to *N*-Boc-4H-Pyridone also failed (entry 12).

Table 4.5 1,4-Conjugate Addition of Functionalized Grignard Reagents to **23**.[28]



23 **24n-t**

n R = $PhCH_2$
o R = 1-napthyl
p R = 4-$Me_2NC_6H_4$
q R = 5-(1-Me)indolyl
r R = 2-$ClCH_2C_6H_4$
s R = vinyl
t R = (*E*)-1-hexenyl
u R = 2-(1-methyl)- imidazoyl
v R = 2-pyridinyl
w R = 1,3-dimethyl-5-uracelyl

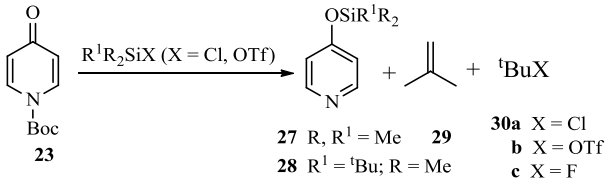
entry	R (equiv)[a]	product	% yields[b]
1	$PhCH_2$ (2.0)	**24n**	81
2	$C_{10}H_7$ (2.0)	**24o**	79
3	*p*-$Me_2NC_6H_4$ (2.0)	**24p**	96
4	5-(1-Me)indoyl (1.2)	**24q**	88
5	2-$ClCH_2C_6H_4$ (1.2)	**24r**	86
6	CH_2=CH (1.2)	**24s**	75
7	C_4H_9CH=CH_2 (1.2)	**24t**	82
8	2-$NO_2C_6H_4$ (2.0)	-	-
9	2-(1-methyl)-imidazoyl (2.0)	-	-
10	2-pyridinyl (2.0)	-	-
11	1,3-dimethyl-5-uracelyl (2.0)	-	-
12	$PhCOCH_2$ (2.0)	-	-

[a] All reactions were run in THF using 1.1-2.0 equiv of RMgX (X = Cl, Br). TMSCl (3.0 equiv) was added as an additive. *N*-Boc-4H-pyridone was added at -78 °C and allowed to warm up the room temperature over 12 hrs. [b] Yields are based on isolated product purified by column chromatography.

After successfully transferring functionalized Grignard reagents in 1,4-conjugate fashion to *N*-Boc-4H-pyridone, the effect of different silanes on the reaction was investigated. These control experiment confirmed that *N*-Boc-4H-pyridone undergo slow *N*-Boc cleavage reaction with 2-4 equivalents of TMSCl (**Table 4.6**, entries 1-7). The cleavage of *N*-Boc group was confirmed by the presence of isobutylene in the ^1H and ^{13}C spectra of the NMR samples (^1H

NMR peak at δ 1.68 and 4.62; ^{13}C NMR peak at δ 24.1, 110.5 and 142.4 ppm). The application of more hindered silane complex such as *tert*-butyldimethyl silyl chloride (TBDMSCl) virtually did not cleave carbamates until 45 minutes (entries 9-13) but slow cleavage was observed when the reaction was left for longer time (entries 14, 15). Not surprisingly, highly reactive trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.0 equiv) cleaved the carbamates instantaneously affording TMS protected 4-hydroxypyridine and isobutylene. The corresponding ^{t}BuOTf was not observed in the reaction.

Table 4.6 NMR Cleavage Study of *N*-Boc-4H-pyridone with Different Silane Reagents.[28]

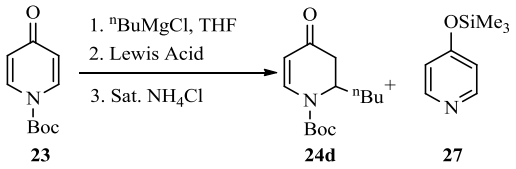


entry	R^1R_2Si X (equiv)	time (h)	NMR ratio **23:27(28):29:30**[a]
1	Me_3SiCl (2.0)	0.08	no rxn
2	Me_3SiCl (2.0)	0.33	94.5:5.5:3.7:1.8
3	Me_3SiCl (2.0)	0.66	91:9:6:3
4	Me_3SiCl (2.0)	1.0	87.3:20.5:13.7:6.8
5	Me_3SiCl (2.0)	2.0	74.1:24.9:16.6:8.3
6	Me_3SiCl (2.0)	3.0	76:24:14:19
7	Me_3SiCl (4.0)	0.08	56.3:43.7:29.1:14.6
8	Me_3SiCl (4.0)	18	0:100:66:33
9	$^{t}BuMe_2SiCl$ (1.0)	0.08	no rxn
10	$^{t}BuMe_2SiCl$ (1.0)	0.33	no rxn
11	$^{t}BuMe_2SiCl$ (1.0)	0.66	no rxn
12	$^{t}BuMe_2SiCl$ (2.0)	0.08	no rxn
13	$^{t}BuMe_2SiCl$ (2.0)	0.66	no rxn
14	$^{t}BuMe_2SiCl$ (2.0)	15	73:(27):14:13
15	$^{t}BuMe_2SiCl$ (2.0)	92	53:(47):22:25
16	Me_3SiOTf (1.0)	0.08	0:100:78:22

[a]The ratio of **29:30** were determined relative to **27** or **28**.

Next, a temperature and time scale study for the completion of the conjugate addition reaction was investigated using different Lewis acids. The temperature screening experiment

Table 4.7 Temperature and Time Screening 1,4-Conjugate Addition Reactions of Grignard Reagents to *N*-Boc-4H-pyridone in the Presence of Lewis Acids.[28]



23 **24d** **27**

entry[a]	Lewis Acid (equiv)	T (°C), h	**24d**, % yield[b]	**23:24d**[c] or (% **27**)[b]
1	TMSCl (2.0)	-23, 1	48	55:45
2	TMSCl (2.0)	-23, 2	53	45:55
3	TMSCl (2.0)	-23, 3	61	30:70
4	TMSCl (1.0)	-78[d]	trace	-
5	TMSCl (3.0)	25, 2	57	-
6	TMSCl (3.0)	25, 3	68	-
7	TMSCl (3.0)	25, 3	47[e]	(41)
8[f]	TMSCl (3.0)	25, 3	55[g]	(37)
9[f]	TMSCl (3.0)	25, 3	73[h]	(13)
10	$BF_3{\cdot}Et_2O$ (2.0)	-78[d]	82	-
11[f]	$BF_3{\cdot}Et_2O$ (2.0)	-78[d]	70	-
12	$BF_3{\cdot}Et_2O$ (1.0)	-78[d]	57	-

[a] The reaction was run using two equivalents of ^{n}BuMgCl unless otherwise noted. [b] Yields are based upon isolated products purified by column chromatography. [c] Determined by NMR integration ratios of the olefin absorptions. [d] Reactions were run at -78 to 25 °C, 12 h. [e] The reaction was conducted in toluene. [f] ^{n}BuMgCl (1.0-1.2 equiv). [g] The reaction was done in $CHCl_3$. [h] The reaction was done in CH_2Cl_2.

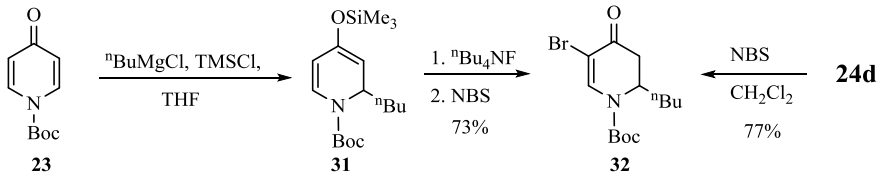
showed that 1,4-conjugate addition of Grignard reagents to *N*-Boc-4H-pyridone does not necessarily need lower temperature as shown in **Table 4.4** and **Table 4.5** but can be carried out at higher temperature (-23 °C) using TMSCl (2.0 equiv) as an additives (**Table 4.7**, entry 1-3) but with lower yields. The reaction failed with 1.0 equivalent of TMSCl (entry 4). The reaction can also be carried out in room temperature using TMSCl (3.0 equiv) in THF affording 1,4-adduct in good yield (entries 5-6). However when non-coordinating solvent like toluene, $CHCl_3$ or CH_2Cl_2 was used, significant amounts of Boc- cleavage product was observed (entries 7, 8 and 9 respectively). The application of $BF_3.OEt_2$ (2.0 equiv) as an additives under identical reaction

conditions unless otherwise noted also delivered good yields of 1,4-adduct (entries 10-11) although lower yield was observed when the amount of $BF_3.OEt_2$ was lowered to 1.0 equivalent (entry 12). A few others Lewis acid such as TMSOTf, TBDMSCl, titanium tetrachloride ($TiCl_4$) and titanium tetraisopropoxide [$Ti(O^iPr)_4$] screened for the 1,4-conjugate addition failed to promote the reaction and delivered either Boc-cleavage products or starting materials.

In order to understand the mechanism of 1,4-conjugate addition reactions of Grignard reagents to *N*-Boc-4H-pyridone in the presence of TMSCl, control experiments were run in the absence or presence of TMSCl. Both of these experiments showed identical ^1H and ^{13}C NMR peaks confirming the absence of complexes or the rapid equlibrium exist between *N*-Boc-4H-pyridone and TMSCl in comparison to NMR time scale. The addition of ^nBuMgCl to the mixture of *N*-Boc-4H-pyridone and TMSCl gave cloudy solution that consumed all Grignard reagents as $–CH_2$-MgCl peak (δ -0.45 (t, 2H)) was absent soon after their addition. However, when the reaction was quenched and worked up, not a trace amount of product was observed. In a second control experiment, $^nBu_4NF$ solution in THF was added to the mixture of *N*-Boc-4H-pyridone, TMSCl and ^nBuMgCl. The solution was turned to colorless which NMR showed the presence of 4-silyloxypyridine **27** resulting from the cleavage of *N*-Boc group along with minor amounts of 1,4-conjugate adduct (~7%) and starting materials (~7%). These experiments lead us to suspect that the presence of trace amounts of DCl in the $CDCl_3$ might play role for cleaving the *N*-Boc group and unavailable for the 1,4-conjugate addition reactions. A control experiment involving the filtration of $CDCl_3$ through basic alumina to remove traces of DCl followed by used for NMR tube experiments gave silyl enol ether consistent with 1,4-conjugate adduct **31** [^{13}C-NMR δ (calcd. value using ACD/NMR predictor software): 162.5 (155.4), 151.0 (153.1) 122.5 (121.5) 114.3 (111.0), 98.4 (109.2), 43.7 (49.1)]. Attempted isolation of silyl enol ether **31** during the reaction of *N*-Boc-4H-pyridone and TMSCl and ^nBuMgCl or conversion of **24d** to corresponding

silyl enol ether treating either with NaH followed by TMSCl in THF/CH_2Cl_2 or Et_3N, TMSCl, DMF, 80 ^oC failed.[29] However, the reaction of intermediate **31** with $^nBu_4NF$ followed by addition of NBS for the trapping of intermediate gave *N*-Boc-5-bromo-2-butyl-2,3-dihydro-4-pyridone **32** in good yields (73%). Product **32** can alternatively be synthesized using literature procedure[17] involving the reaction of **24d** with NBS with slightly better yields (**Scheme 4.5**).

Scheme 4.5 Attempted in situ Trapping of 1,4-Adduct and Bromination Reactions.[28]



4.32 Synthesis of 2,6-Disubstituted Piperidinones

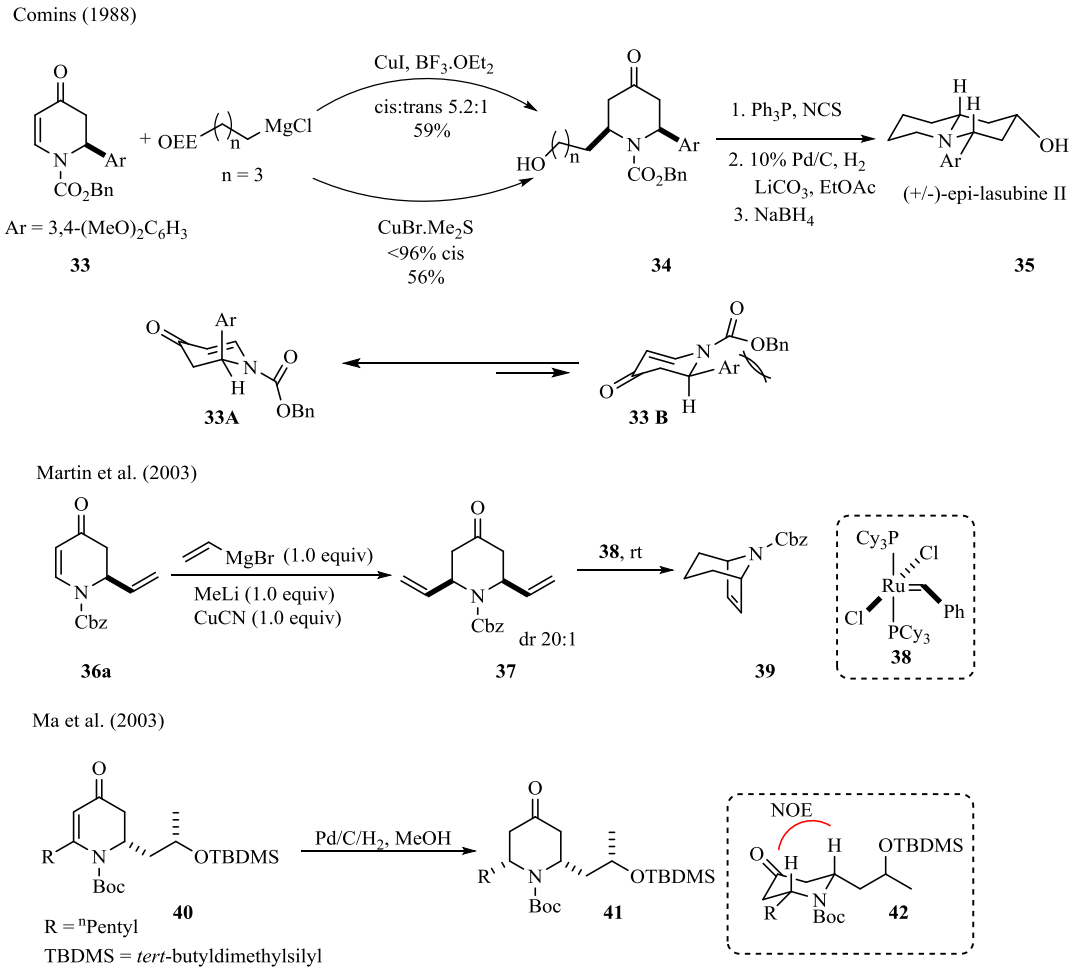
2-Substitued-2,3-dihydropyridones are highly versatile synthons that can undergo further 1,4-conjugate addition reaction with organometallic reagents in the presence of additives affording (*Z)*- and/or (*E)*- 2,6-disubstituted piperidinone derivatives.[6, 22] It was widely reported that tetrahydropiperidinone exist in boat, twist boat or chair conformations. Addressing the stereochemistry of the 2,6-disubstituted piperidinone is a big challenge due to the conformational changes exist in the molecule.

All existing methodologies for the synthesis of 2,6-disubstituted-4-piperidinone involved the reaction of organometallic reagents with 2-substituted 2,3-dihydropyridone in the presence of stoichiometric or catalytic amounts of copper(I) salts. In 1988, Comins and coworkers[21] reported the copper catalyzed 1,4-conjugate addition reaction of Grignard reagents to 2-aryl substituted

2,3-dihydro-4-pyridone **33** using $BF_3.OEt_2$ as additives under different reaction conditions (**Scheme 4.6**). The reaction gave corresponding product **34** in moderate yield under optimized reaction conditions (78 ^oC, THF, 3h, 59%, *cis:trans*, 5.2:1). The modification of procedure employing $RCu.BF_3$ derived from 4-chlorobutylmagnesium bromide with dihydropyridone **33** gave high *cis* stereoselectivity (>96%) maintaining similar yields (56%). To the contrary, utilization of CuI under identical reaction conditions dropped the stereoselectivity to 0%. Authors claimed that the presence of $A^{1,3}$ strain between the equatorial aryl group with *N*-acyl group in chair conformation of **33A** forced the aryl group in axial conformation and the stereo-electronically favored axial attack of organocuprate reagents to the enone moiety gave major cis-1,4-adduct **34**. The stereochemistry of the 2,6-disubsituted product was unambiguously determined by converting into natural products (+/-)-*epi*-lasubine II. Martin and Neipp[30] reported copper catalyzed conjugate addition reaction of vinyl Grignard reagents to 2-vinyl substituted 2,3-dihydropyridone **36a** affording the mixture of *cis* and *trans* 2,6-dialkenyl-*N*-acyl piperidinone derivatives **37** in good yields. The stereochemistry of the product was determined by performing the ring closing metathesis (RCM) reactions of **37** into **39** using catalytic amounts of Grubbs first generation catalyst **38**. The author claimed that 2,6-vinyl substituents in **37** preferred the axial conformation in order to minimize the $A^{1,3}$ strain with *N*-acyl group. The axial orientation of two vinyl group facilitated the RCM reaction affording bridged bicyclic compound **39**. RCM product **39** is structural subunits of several natural and unnatural products.[31] Ma and coworkers[32] reported palladium catalyzed hydrogenation reaction of **40** affording cis 2,6-disubstituted-4-pipperidinone **41**, a subunit of over fifty known ladybird alkaloids. In accordance with Comins and coworkers claimed,[21] severe $A^{1,3}$ strain between the 2-alkyl substituent with *N*-Boc group was proposed in the reaction that enforces the alkyl substituent in the axial position. The preferred axial reduction

of double bond gave the *cis* 2,6-disubstituted piperidinone in quantitative yields. The stereochemistry of the product **42** was confirmed by a strong NOE effect between H2 and H6.

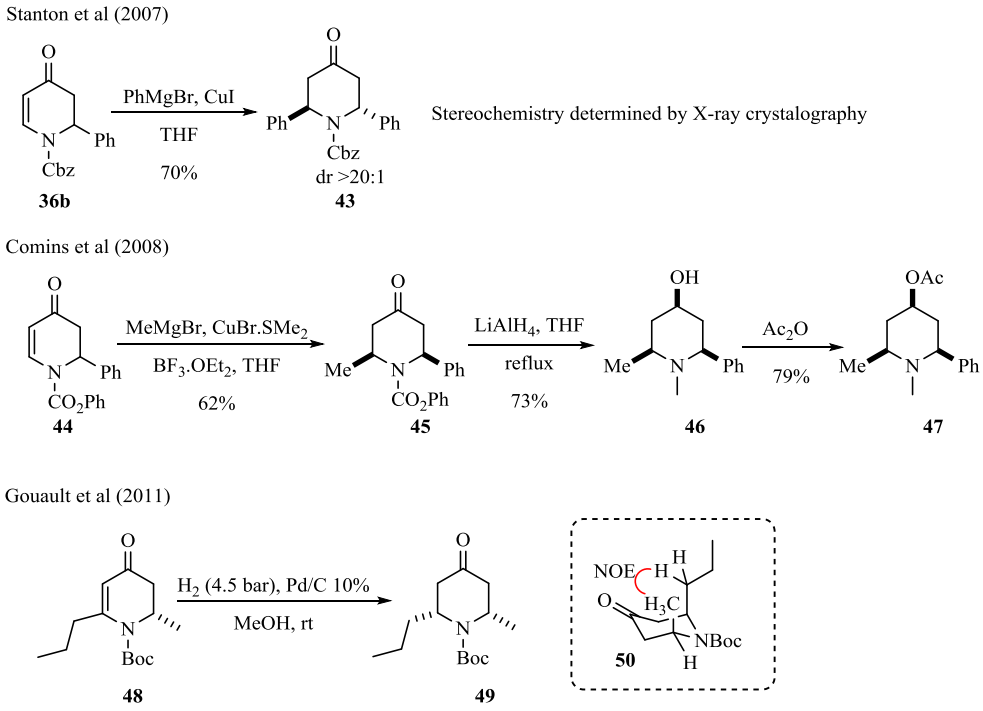
Scheme 4.6 Synthesis of *cis*-2,6-Disubstituted 4-Piperidinones.[21,30,32]



A diastereoselective method for the synthesis of *trans*-2,6-diphenyl-4-piperidinone **43** was reported by Stanton and coworkers[33] during the copper (I) iodide catalyzed 1,4-conjugate addition of phenylmagnesium bromide to 2-phenyl-2,3-dihydro-4-pyridone **36b**. The application of a variety of electron rich and electron deficient aryl Grignard reagents gave similar yields under identical reaction conditions. The twist boat conformation of the piperidine ring present in

both starting material and product was assigned by single crystal X-ray analysis. The authors claimed that phenylmagnesium bromide preferred axial attack to the twist boat conformation of 2-phenyl-2,3-dihydro-4-pyridone from the face away from existing phenyl group gave *trans* **43**. The twist boat conformation also eliminated the severe $A^{1,3}$ strain that exist in corresponding chair conformations. One year later, Comins and coworkers[23] reported a copper catalyzed 1,4-addition reaction of methylmagnesium bromide to 2-aryl-2,3-dihydropyridone in the presence of $BF_3.OEt_2$ as an additives affording cis 2-aryl-6-methyl-4-piperidinone in moderate yield and good diastereoselectivity (62%, *cis*:*trans* 5:1). The *cis*-stereochemistry of preferentially formed diastereomer was determined by converting **45** into **47** followed by their NOESY experiments. In NOESY experiment, both H2 and H6 hydrogen showed strong NOE effect with carbinol hydrogen (i.e., H_4) confirming the cis-stereochemistry of the product. Gouault[34] recently reported the synthesis of cis 2,6-dialkyl substituted 4-piperidinone **49** using catalytic hydrogenation of **48**. The stereochemistry of the product was determined by NOESY experiment of **49** where strong NOE effect between methyl hydrogen at C6 with the 1'-CH_2 hydrogen of propyl substituents as shown in **51** confirmed the *cis* stereochemistry.

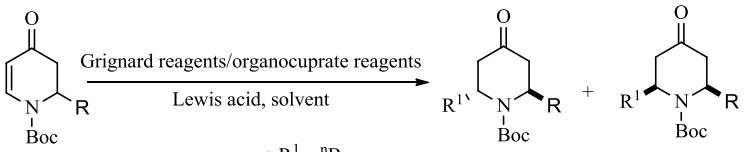
Scheme 4.7 Synthesis of *cis*- and *trans*-2,6-Disubstituted-4-Piperidinone.[23,33,34]



Motivated from these literature results, 1,4-conjugate addition of Grignard reagents to 2-substituted 2,3-dihydropyridone using TMSCl as an additives was investigated in our laboratory. The reaction of ^{n}BuMgCl or $^{n}Bu_2CuLi$ with 2-(2-methylphenyl)-2,3-dihydropyridone **25j** in the presence of TMSCl (3.0 equiv) in THF gave a single isomer **51a** in good yield (**Table 4.8**, entries 1 and 2). However the reaction of ^{n}BuMgCl in the presence of CuI (1.0 equiv) and $BF_3.OEt_2$ (0.5 equiv) using modified Comin's procedure[21] gave the mixture of 2,6-disubstituted-4-piperidinones **51a** and **52a** (2:1 ratio, entry 3). ^{i}PrMgBr and $PhCH_2MgBr$ on reaction with **24j** gave a single isomer of *trans*-2,6-disubstituted-4-piperidinones **51b** and **51c** respectively (entries 4 and 5). Although, the reaction of ^{n}BuMgCl with 2-*n*-butyl-2,3-dihydropyridone **25d** in the presence of TMSCl (3.0 equiv) gave *trans*-2,6-*n*-dibutyl substituted pyridone **53a** (entry 6), employment of

$^{n}Bu_2CuLi.Me_2S$ gave *cis*-2,6-*n*-dibutyl substituted pyridone **54a** exclusively (entry 7). Application of $^{i}PrMgBr$ for the reaction with **24d** also gave **53b** in excellent yields under identical reaction conditions (entry 8).

Table 4.8 Diastereoselective 1,4-Conjugate Addition to 2,3-Dihydropyridone.[28]



entry	SM	reagents (equiv)	Lewis acid (equiv)	solvent	product	% yield[a]	dr **A:B**
1	**24j**	$^{n}BuMgCl$ (1.2)	TMSCl (3.0)	THF	**51a**	88	100:0
2	**24j**	$^{n}Bu_2CuLi.Me_2S$ (2.0)	TMSCl (3.0)	Et_2O	**51a**	88	100:0
3	**24j**	$^{n}BuCuMgCl$ (1.1)	$BF_3.OEt_2$ (0.5)	Et_2O	**51a+52a**	82	60:40
4	**24j**	$^{i}PrMgBr$ (1.2)	TMSCl (3.0)	THF	**51b**	85	100:0
5	**24j**	$PhCH_2MgBr$ (2.0)	TMSCl (3.0)	THF	**51c**	89	100:0
6	**24d**	$^{n}BuMgCl$ (1.2)	TMSCl (3.0)	THF	**53a**	89	100:0
7	**24d**	$^{n}Bu_2CuLi.Me_2S$ (2.0)	TMSCl (3.0)	Et_2O	**54a**	86	0:100
8	**24d**	$^{i}PrMgBr$ (1.2)	TMSCl (3.0)	THF	**53b**	88	100:0

[a] Yields are based upon isolated products after flash column chromatography.

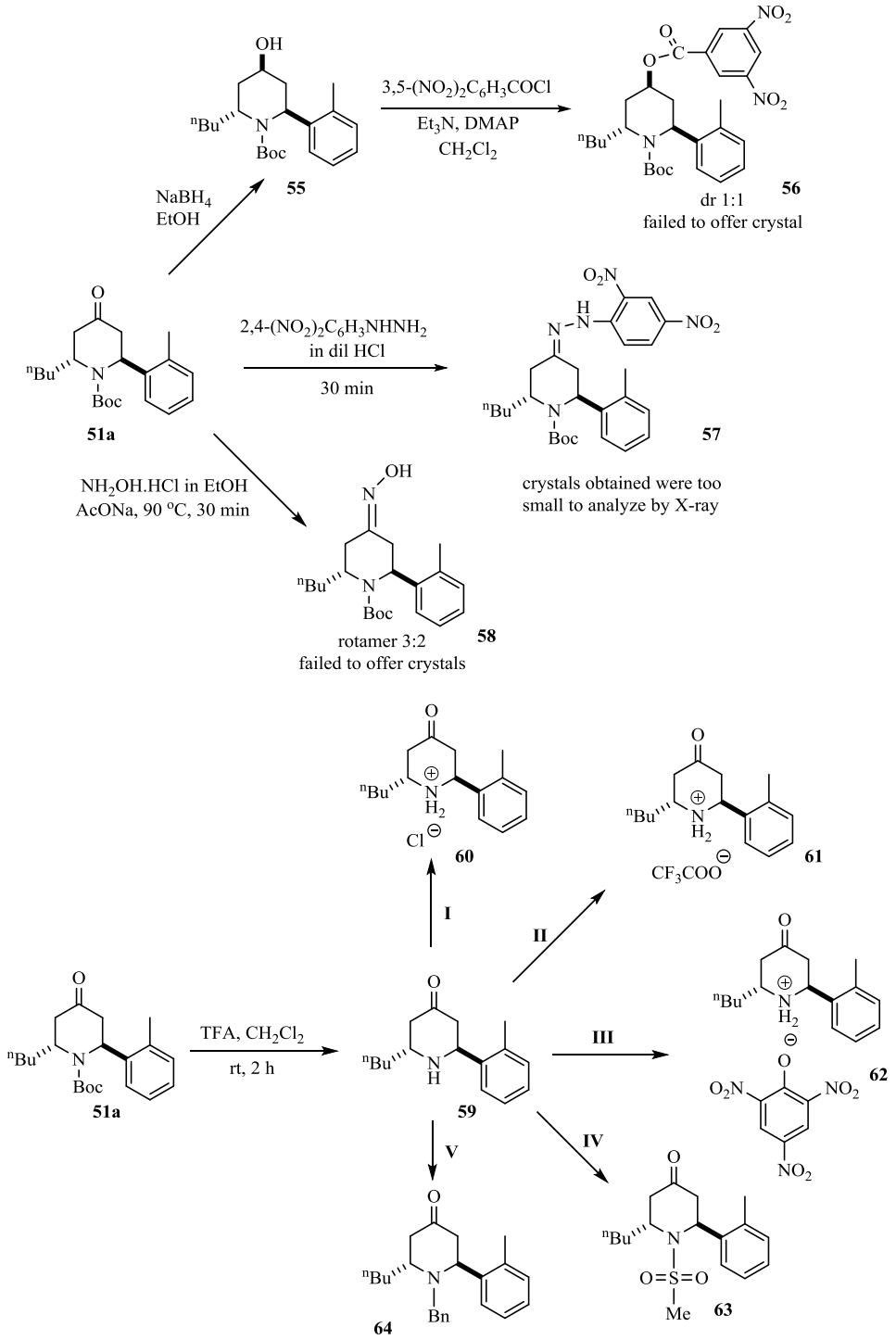
Although, the stereochemistry of 2,6-disubstitued piperidinone was determined by NOESY experiment previously,[23,32,34] we failed to establish the stereochemistry of disubstituted piperidinones **51-54** using conventional NOESY experiment. Compounds **51a-c** showed two distinct ^{1}H NMR peak for methine hydrogen adjacent to *N*-atom. But in the case of 2,6-di-*n*-butyl piperidinone; **53a** showed a single broad peak at δ 4.09 while **54a** showed broad peak at δ 4.95. Compound **53a** was an exclusive product in the reaction of $^{n}BuMgCl$/TMSCl with **24d** and **54a** was the only product observed in TMSCl reaction. However, both products **53a** and **54a** gave

only four ^{13}C NMR signals for both butyl groups. The difference in the chemical shift for methine hydrogen quickly ascertained us that compounds **53a** and **54a** were different stereoisomer and the complete identification was essential for the determination of their relative stereochemistry.

The reduction of **51a** to **55** followed by converting into 3,5-dinitrobenzoyl derivatives **56** or converting **51a** into 3,5-dinitrobenzoyl hydrazone **57** or oxime **58** did not offer good crystals for X-ray crystallography. On the other hand, deprotection of *N*-Boc group into free amine **59** followed by conversion into HCl, CF_3COOH or picrate salts (**60-62** respectively) or the protection of free amine **59** with benzyl group ($PhCH_2Br$, K_2CO_3, rt, 12h)[35] and sulfonyl group ($MeSO_2Cl$, Et_3N, CH_2Cl_2, 12 h)[36] also did not give good crystals for X-ray crystallography.

However, crystals suitable for X-ray crystallography was achieved for 2,6-disubstituted-4-piperidinone **51c** in Et_2O and the *trans*-stereochemistry of the product was assigned. The structure of the molecule **51c** is shown in **Figure 4.6** as 50% probability thermal ellipsoids. Specifically, the presence of a torsion angle of 177.12 (1)° between the bonds connecting the tolyl group and the benzyl group to the central piperidinone ring indicated a *trans* arrangement of these groups. In this structure, the individual aromatic rings themselves are approximately planar, but their planes are oriented about 105° relative to one another. The central piperidine ring is somewhat distorted and adopted a twist-boat conformation. Although, the solution state conformation of the compound does not necessarily mirror the solid state structure, the twist-boat conformation of **51c** was also expected in the solution too.

Scheme 4.8 Synthesis of Different Derivatives of 2,6-Disubstitued 4-Piperidinone.

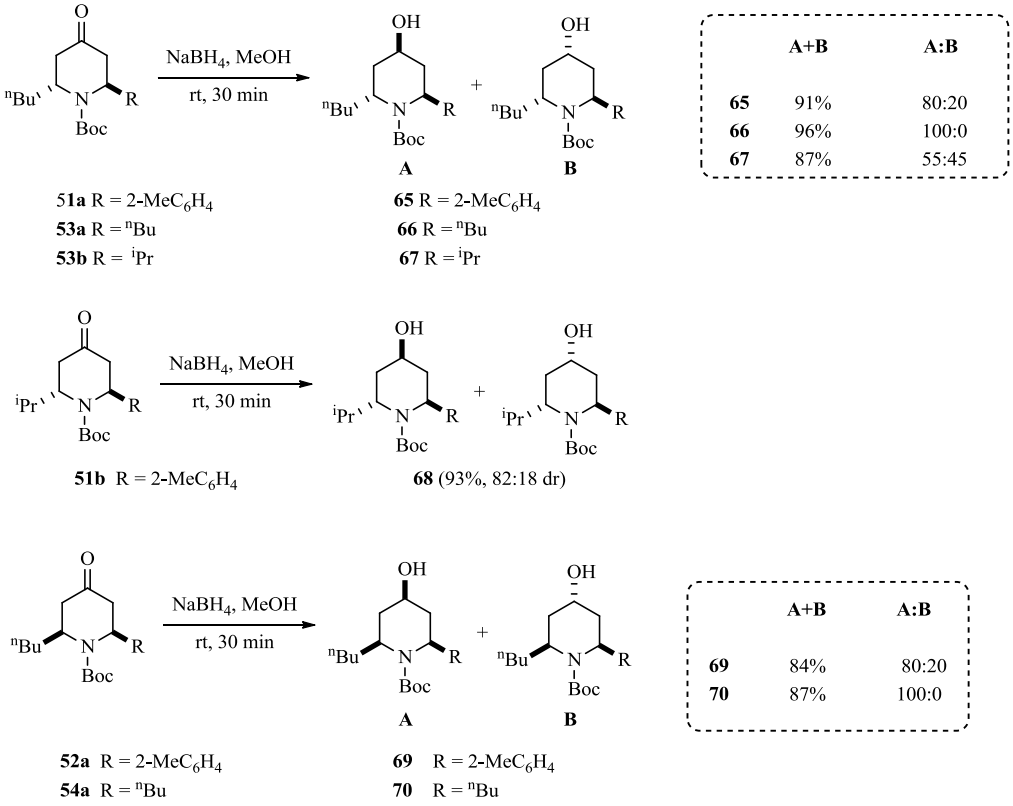


I. 10% HCl, CH_2Cl_2, rt, 30 min **II.** CF_3COOH, CH_2Cl_2, rt, 30 min **III.** Picric acid, EtOH, 60 °C, 30 min

IV. $MeSO_2Cl$, Et_3N, CH_2Cl_2, 12 h **V.** $PhCH_2Br$, K_2CO_3, rt, 12h

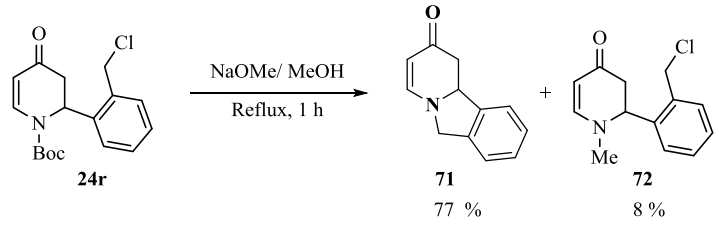
In order to determine the stereochemistry of the 2,6-disubstituted-4-piperidinone, compounds **51-54** were reduced to corresponding alcohols **65-69** (dr 55:45-100:0) using the standard literature procedure (**Scheme 4.9**).[23] The NOESY experiment of major alcohols **65, 67, 68** showed a strong correlation between H2 and H4 but absence of such correlation between H6 and H4 confirming the *trans*-stereochemistry. On the other hand, 2,6-disubstitued 4-piperidinol **69** showed strong NOESY correlation between H2 (hydrogen attached to tolyl group) with H4 as well as H2 with H6 confirming their *cis* stereochemistry. The absence of symmetry in piperidinol **66** showed two absorption peaks for methine hydrogen adjacent to nitrogen in ^{1}H NMR and two sets of carbon absorptions for both butyl group in ^{13}C-NMR confirmed the trans-stereochemistry. On the other hand, piperidinol **69** displayed single methine absorption peak in ^{1}H NMR and one set of carbon absorption for both butyl group in ^{13}C-NMR confirmed their cis-stereochemistry.

Scheme 4.9 Reduction of *trans*- and *cis*- 2,6-Disubstituted 4-Piperidinone.[28]



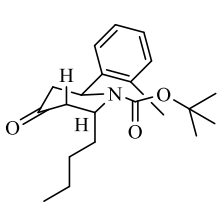
The versatility of the 2-aryl substituted 2,3-dihydropyridone was illustrated by the successful conversion of **24r** into bicyclic compounds **71** and **72** on refluxing with sodium methoxide in methanol for one hour (**Scheme 4.10**).

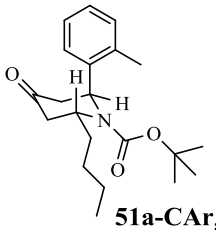
Scheme 4.10 Cyclization of **24r** to Tricyclic Compound **71**.[28]

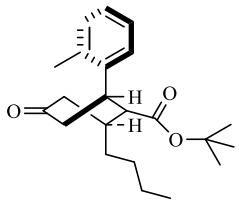


4.33 Computational Calculations for the Transition State Energy of 2,6-Disubsituted Piperidinones and Piperidinols

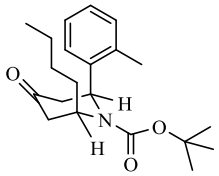
To check the feasibility of the reaction and established the conformation of piperidine ring present in the products, a theoretical study for the chair and boat conformations of *cis* and *trans*-2,6-disubstituted-4-piperidinones and corresponding 4-piperidinols was carried out.[28] Semi-empirical calculations using AM_1 and PM_3 gave inconsistent results while *ab initio* calculations using Hartree Fock (HF, 6-31 G*) and Density Functional Theory (DFT, B_3LYP, 6-31G*) gave consistent results for boat and chair conformations of 2,6-disubstituted-4-piperidinone (**Figure 4.2**).[28] The *ab initio* calculation using HF and DFT of *trans*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone **51a** showed the chair conformation involving axial 2-methylphenyl group and equatorial *n*-butyl group (i.e., **51a-CAr$_{ax}$**) has lowest energy compared to chair conformation involving equatorial 2-methylphenyl group and axial *n*-butyl group (i.e., **51a-CR$_{ax}$**) and twist boat conformation (**51a-TB$_{diax}$**).

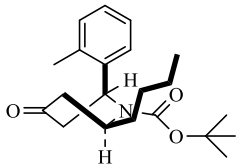


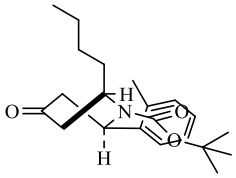




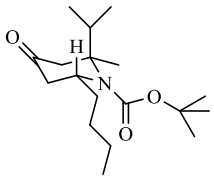
	51a-CR$_{ax}$	**51a-CAr$_{ax}$**	**51a-TB$_{diax}$**
AM1	0.00	-2.08	-3.00
PM3	-0.59	-0.96	0.00
HF (6-31G*)	0.00	-10.29	-3.33
DFT (B3LYP)	0.00	-8.16	-6.97

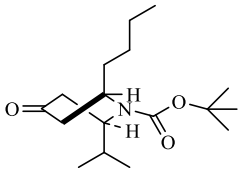




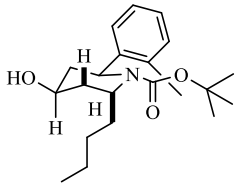


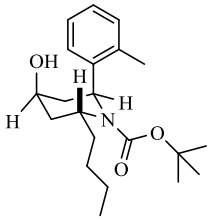
	52a-Cdi$_{ax}$	**52a-TBAr$_{ax}$**	**52a-TBR$_{ax}$**
HF (6-31 G*)	-2.89	-3.07	0.00
DFT (B3LYP)	-5.96	-2.51	0.00

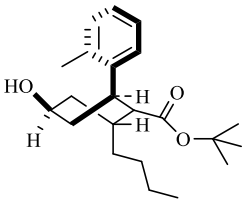




	53b-Cdi$_{ax}$	**53b-TB$_{diax}$**
AM1	0.00	-1.32
HF (6-31G*)	0.00	-3.50







	65-CR$_{ax}$	**65-CAr$_{ax}$**	**65-TB$_{diax}$**
AM1	-0.42	-0.64	0.00
PM3	-2.20	-3.68	0.00
HF (6-31G*)	0.00	-4.52	-7.59
DFT (B3LYP)	0.00	-3.45	-6.53

Ar = aryl, R = alkyl, C = chair, TB = twist boat ax = axial diax = diaxial

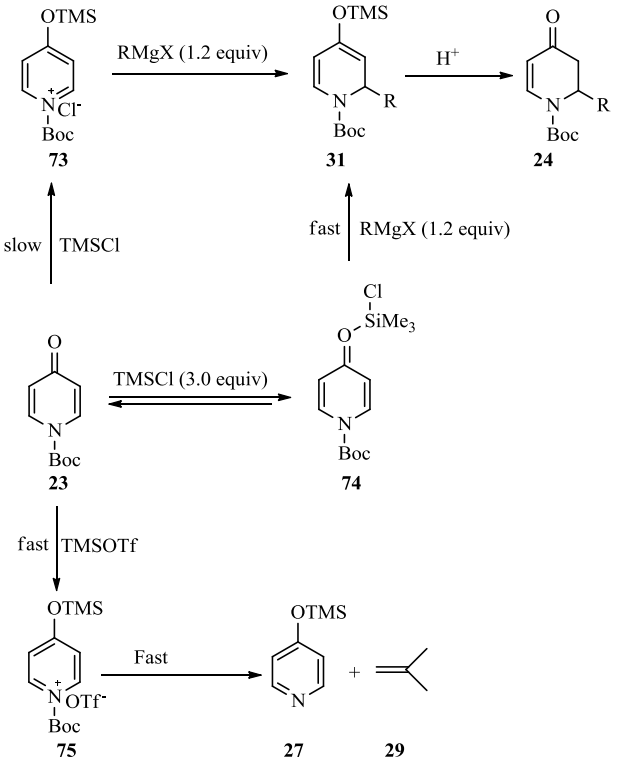
Figure 4.2 DFT, HF, AM1 and PM3 Energy Calculation of Chair and Twist Boat Conformations of **51a**, **52a**, **53b** and **65**.Reprinted with permission from *J. Org. Chem*. **2013**, 78, 8451-8464. Copyright (2013), American Chemical Society.[28]

HF calculation for *cis*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone **52a** showed twist boat conformation bearing axial 2-methylphenyl group and equatorial *n*-butyl group (i.e., **52a-TBAr$_{ax}$**) has most stable conformation than other twist boat conformation **52a-TBR$_{ax}$** and chair conformation **52a-C$_{diax}$**. On the other hand, DFT calculation showed chair conformation **52a-C$_{diax}$** is more stable than the **52a-TBAr$_{ax}$** and **52a-TBR$_{ax}$**. HF calculations for the *trans*-*N*-Boc-2-(1-methylethyl)-6-butyl-tetrahydropyridone **53b** showed boat conformation **53b-TB$_{diax}$** has relatively more stable than corresponding chair conformation **53b-C^{i}Pr$_{ax}$**. Besides, HF and DFT calculation of chair and boat conformations of *trans*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinol **65** predicted twist boat conformation **65-TB$_{diax}$** is more stable than the corresponding chair conformations **65-CR$_{ax}$** and **65-CAr$_{ax}$**. The 1,4-twist conformation shown in **Figure 4.3** were expected to be in equilibrium with 2,5-twist and 3,6-twist boat conformations.[37] It was expected that several closely lying conformational minima exist via pseudorotation about the ring atoms and some of which displayed NOE effects (i.e., generally internuclear distances <3.5Å).[28]

4.4 Discussion

The addition of Grignard reagents to 4H-pyridones **23** and **25** in the presence of TMSCl principally can undergo either 1,4-conjugate addition to the enone or 1,2-addition to the in situ generated pyridinium salts. Although, Comins and coworkers[6, 17, 18, 20] reported several examples for the 1,2-addition of organometallic reagents to pyridinium salts, the cleavage of Boc-group while using TMSOTf as an additives in our study suggested that pyridinium ion was not the intermediate in the reaction. An alternative mechanism involved the formation of pyridone-TMSCl complex which activated the 4-pyridone towards conjugate addition reaction. This result was further confirmed by our NMR control experiments where the application of TBDMSCl as an additive failed to promote the reaction and the use of highly reactive silanes (i.e., TMSOTf) cleaved the Boc-group instantaneously into silyl enol ether **27** and isobutylene **29**. Although, pyridones **23** is vinylogous amide that is prone to undergo complex formation with TMSCl than simple enones, we failed to isolate such complex or to identify the complex by NMR spectroscopy probably due to low concentration of complex in the solution or the rapid equilibration between complex and uncomplexed species.[28]

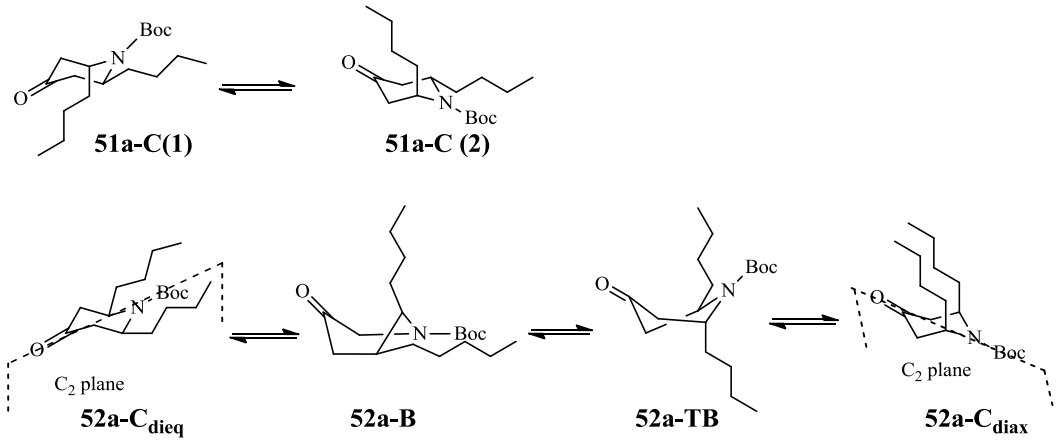
Scheme 4.11 Mechanistic Study of 1,4-Conjugate Addition Promoted by Lewis Acids.[28]



The issue of 1,2- vs. 1,4- addition is then largely a matter of semantics since formation of a TMSCl-pyridone complex before or during the Grignard addition enhances the electrophilic character of the enone β-carbon atom, which will also have a resonance contributor involving the carbamate *N*-lone pair. Although, we were unable to definitively identify this complex in the NMR studies, the need for 2-3 equivalents of TMSCl in order to obtain good yields of conjugate adducts is suggestive of formation of such a complex in a bimolecular or termolecular process. Partitioning between carbamate cleavage and Grignard addition can be subtlety influenced by reaction conditions (e.g., solvent and temperature).[28]

The difficulty in the determination of stereochemistry of *N*-Boc-2,6-disubstitued-4-pipperidinone was highly challenging due to the rapid conformational changes among chair, twist

boat and boat of the piperidinone rings. This result was also supported by the literature assignments involving NOESY experiments.[32,34] A single set of NMR absorptions for both *trans*- and *cis*-2,6-di-*n*-butyl-4-piperidinone **51a** and **52a** was rationalized due to the rapid equilibrium between two chair conformation via several closely lying twist boat or boat conformations where NMR did not distinguish the axial and equatorial *n*-butyl groups. Besides, **52a** bear plane of symmetry and hence both butyl groups were indistinguishable in NMR time scale.

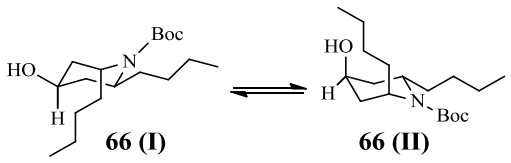


C = chair B = boat TB = twistboat dieq = diequitorial diax = diaxial

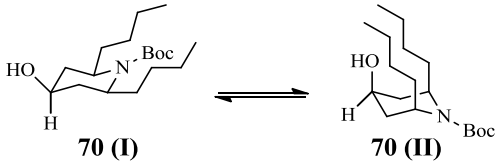
Figure 4.3 Equilibrium Structures of *cis*- and *trans*- 2,6-Di-*n*-butylpiperidinone.

The reduction of compound **53a** and **54a** using standard reduction procedure gave corresponding 4-piperidinol derivatives **66** and **70** respectively. The ^{1}H NMR of **66** showed two methine absorption for hydrogen adjacent to *N*-atom and two sets of carbon absorptions for two *n*-butyl group in ^{13}C NMR confirming the *trans* stereochemistry. This result was further supported by the NOESY experiment of *trans*-2,6-dibutyl-4-piperidinol **66** where one of the methine hydrogen adjacent to *N*-atom showed strong NOE effects with carbinol hydrogen while the other methine hydrogen did not show NOE effect. To the contrary, observation of single set of

methine hydrogen absorption in ^{1}H NMR and single set of ^{13}C NMR absorption for both *n*-butyl group of **70** confirmed the *cis* stereochemistry of 2,6-substituted butyl groups.

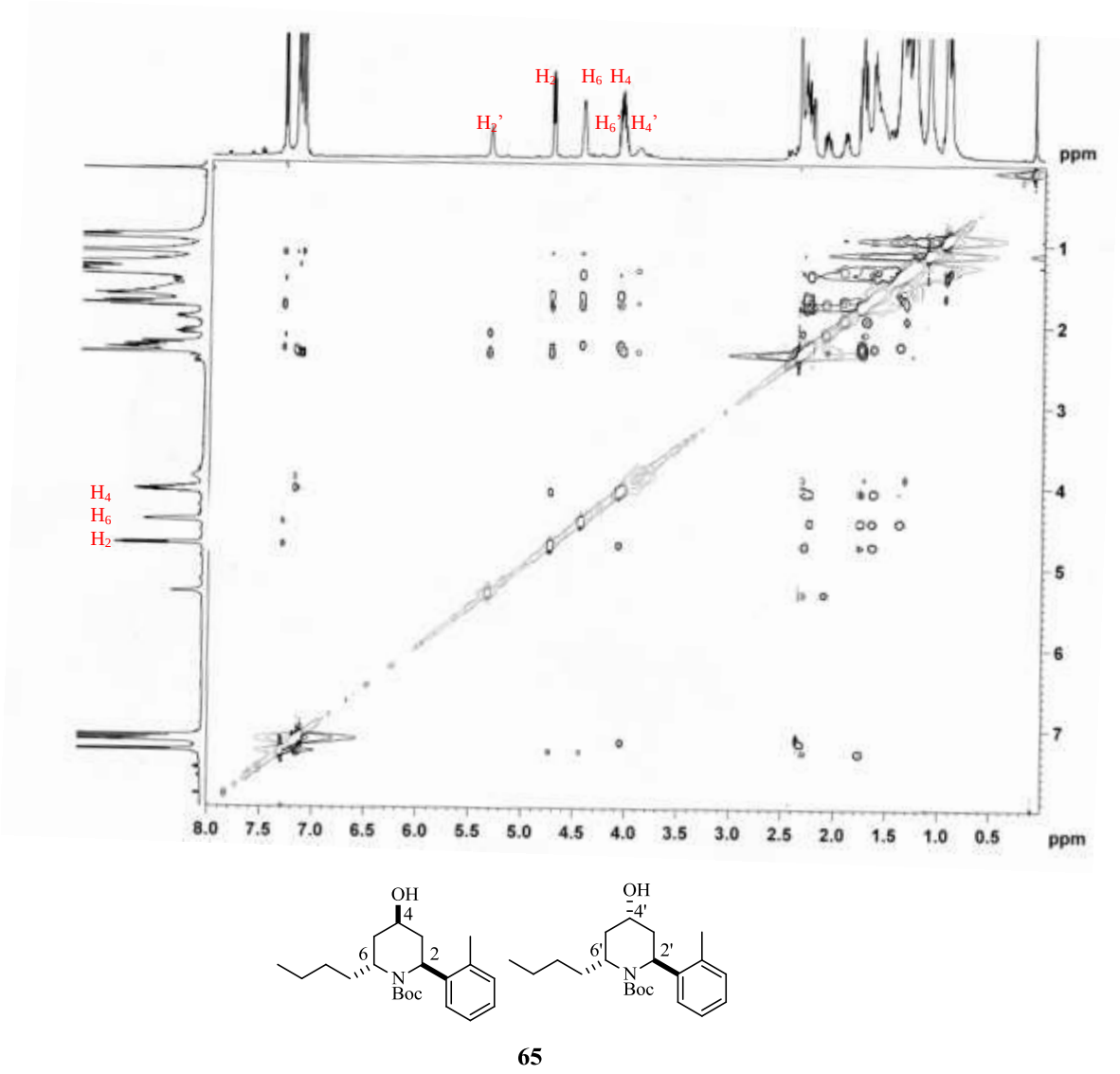


Two sets of ^{1}H and ^{13}C peak for butyl groups



Only one set of ^{1}H and ^{13}C peak for butyl groups

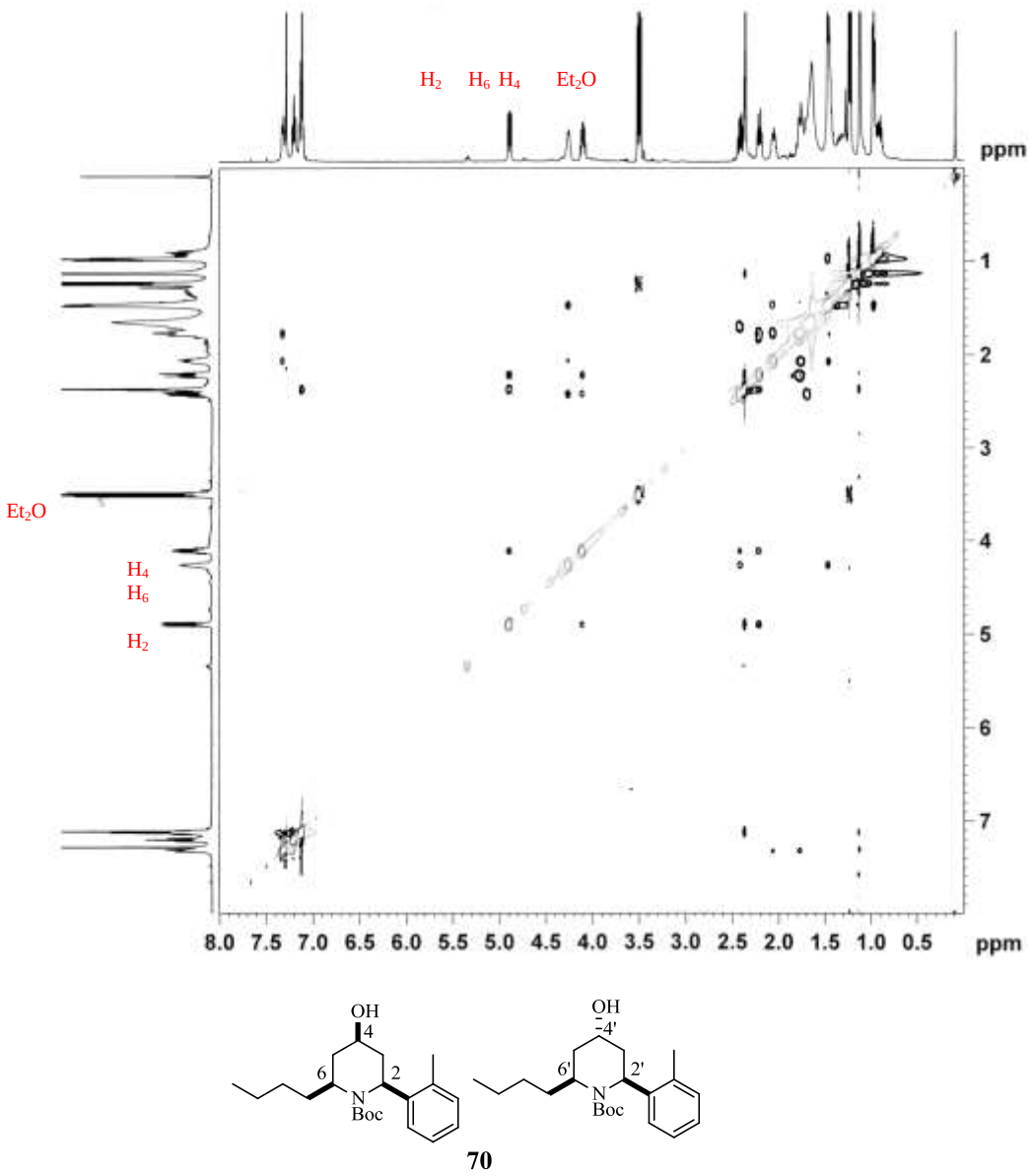
Accordingly, compounds **51a** and **52a** were reduced to corresponding piperidinols **65** and **69** and employed for the COSY and NOESY experiment. The H2, H4 and H6 hydrogens in the piperidinol ring were assigned using COSY experiments for both *cis*- and *trans*-2-tolyl-6-*n*-butyl-4-piperidinol **65** and **69** respectively. The COSY experiment confirmed that methine hydrogen attached to tolyl group was down fielded (δ 4.65 ppm and δ 4.90 ppm for the major isomer of **65** and **69** respectively) with respect to the methine hydrogen attached to *n*-butyl group (δ 4.35 ppm and δ 4.20 ppm for the major isomer of **65** and **69** respectively). A minor amount of diastereomeric piperidinol derivatives was also observed in the reaction during the reduction of 4-piperidinone derivatives **51a** and **52a**. The NOESY spectrum of *trans*-2-tolyl-6-*n*-butyl-4-piperidinol **65** showed strong NOE effect between H2 and H4 confirming their *cis*-stereochemistry but H6 did not show NOE effect with H4. This result confirmed the *trans*-stereochemistry of piperidinol **65** (**Figure 4.4**).



65

Figure 4.4 NOESY NMR of *trans*-2-tolyl-6-*n*-butyl-4-piperidinol **65**.

To the contrary, NOESY experiment on *cis*-2-tolyl-6-*n*-butyl-4-piperidinol **69** showed strong NOE effect of H2 with both H4 and H6 hydrogens confirming their *cis*-stereochemistry (**Figure 4.6**).



70

Figure 4.5 NOESY NMR of *cis*-2-tolyl-6-*n*-butyl-4-piperidinol **69**.

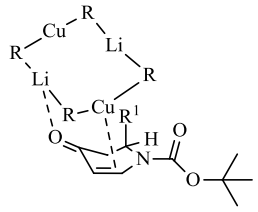
The *trans* stereochemistry of piperidinol derivatives **67** and **68** were also confirmed by NOESY experiments accordingly. The higher regioselectivity observed in the reduction of *cis* and *trans* 2-tolyl-6-*n*-butyl-piperidinone **51a** and **52a** can be rationalized due to the higher A values

for the tolyl group in either the boat or chair conformation while the lack of stereoselectivity in the reduction of **53b** probably due to the comparable A-values for ^{n}Bu and ^{i}Pr substituent.[28]

The formation of *trans*-isomer in the reaction of Grignard reagents with 2-substituted 2,3-dihydropyridone possibly arise from the enone-TMSCl complexes where Lewis acid was not associated with the enone hence conjugate addition reaction preferred from the less hindered concave face of the six member ring probably due to steric reason. To the contrary, cuprate reagents usually preferred to undergo coordination with the carbonyl group via the metal (e.g., Li^{+} or MgX^{+}) hence conjugate addition usually occur from the side of axial substituent in a half chair conformations of the six member ring. Previously few methods for the synthesis of *cis*-[21, 23, 30] and *trans*-substituted[33] 2,6-tetrahydropyridones during the copper mediated conjugate addition reactions to 2-aryl-2,3-dihydropyridones were reported. AM1 semi-empirical calculations employing MacSpartan confirm that the axial conformer for both **24b** and **24d** is more stable than the equatorial conformer by 2.0-2.6 Kcal/mole. Additionally, both have roughly the same conformation of the pyridone ring, which is closer to a chair conformation than to a half-boat. The supposition of a half-boat conformation was predicated on an X-ray structure,[33] which need not mirror solution conformations. The cis/trans-stereochemical outcome of the conjugate addition reactions seems to reflect the steric hindrance of both the 2-substitutent on the 2,3-dihydropyridone and the ligand on the organometallic reagents. As suggested by Comins and coworkers[21] the equatorial orientation of 2-methylphenyl group developed severe $A^{1,3}$ strain with *N*-Boc substituent and forces the 2-methylphenyl group in the axial position followed by axial attack of organocuprate reagents may lead to cis-2,6-disubstituted products. But as our work and that of Hamblett and co-workers[19] showed this stereo electronic preference can be circumvented by the cumulative steric hindrance of the 2-substitutent on the 2,3-dihydropyridone and the organometallic ligand to afford the trans-diastereomer. It's noteworthy that not a single factor

may control the outcome of the reactions however arises from the interplay between multiple factors. Some other factors like the geometry of organocuprate reagents (e.g., homodimer in Et_2O and heterodimer in THF), the counter ion present in the cuprate reagents (e.g., Li^+ or MgX^+), the C2-C3-C4-C5 dihedral angle in the substrates may influence the stereochemistry of 2,6-disubstitued piperidinones.[28]

Table 4.9 Transition State Model for the Attack of Organocuprate and Grignard Reagents to 2,3-Disubstituted Dihydropyridone.[28]



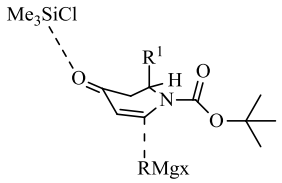
Dihedral angle: C2-C3-C4-C5

24d R^1 = ^{n}Bu 10.4 °

24b R^1 = Ph 7.8 °

24j R^1 = O-MeC_6H_4 13.3°

33 R^1 = 3,4-$(MeO)_2C_6H_3$ 9.7 °



trans product in all cases

$R^1 = CH_2CH=CH_2$ 9.1 °

R^1, R: Cu reagents and reaction conditions	cis:trans (R^1, R)[ref]
R^1 = 3,4-$(MeO)_2C_6H_3$; R = $Cl(CH_2)_4$: $R_2CuMgCl$ (?), THF	3:1[21]
RCu or RCuBrMgBr/ $BF_3.OEt_2$, THF	4.7:1[21]
R^1 = Ph; R = Me MeCu or MeCuBrMgBr/$BF_3.OEt_2$, THF	5:1[23]
R^1 = *o*-MeC_6H_4; R = ^{n}Bu ^{n}BuCu or ^{n}BuCuIMgX/$BF_3.OEt_2$, THF	1:1.5[a]
$^n Bu_2CuLi$, Me_2S, Et_2O	1:99[a]
R^1 = R = Ph: R_2CuMgX, THF	1:20[33]
$R^1 = CH_2CH=CH_2$; R = CH_2CH_2 MeCuR)M [M = Li or MgX], THF:Et_2O (3:1)	20:1[30]
$R^1 = CH_2CH=CH_2$; R = CH_2CHCH_3 : MeCuR)M [M = Li or MgX], THF:Et_2O (3:1)	9:1[30]
R^1 = ^{n}Bu; R = $^n Bu_2CuLi$, Et_2O	99:1[a]

[a] Present work

4.5 Conclusion

In summary, a highly successful method for the 1,4-addition reactions of Grignard reagents to *N*-carbamoyl-4-pyridones using TMSCl as an additives in the absences of Cu(I) was explored during our investigation.[28] A large numbers of non-functionalized and functionalized alkyl, aryl, and vinyl Grignard reagents were transferred with high yields affording 2-substituted-2,3-dihydropyridones which are structural subunits of several piperidones, piperidines, indolizidenes, and quinolizidenes bearing natural products.[6] The second 1,4-addition of Grignard reagents or cuprates to 2-substituted-2,3-dihydropyridones gave highly diastereoselective cis or trans 2,6-disubstituted tetrahydropyridones. Theoretical studies using DFT and HF calculations of 2,6-disubstititued-4-piperidinones provided new insight into reactivity pattern of different organometallic reagents with 2-substituted-2,3-dihydropyridones leading to cis or trans products arising from the conformational changes exist in the molecule. The enantioselective conjugate addition reactions of Grignard reagent to *N*-carbamoyl-4-pyridones provides new avenue for the synthesis of 2-substituted-2,3-dihydropyridones if successfully implemented our protocol in future.

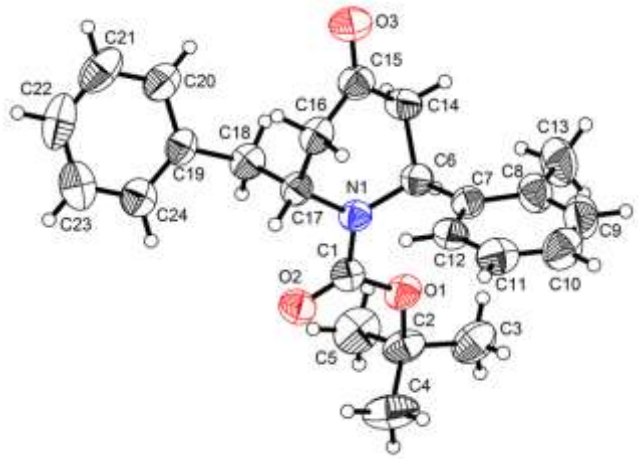


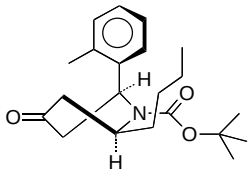
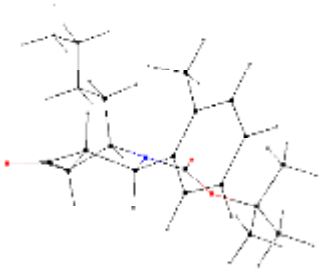
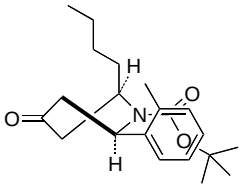
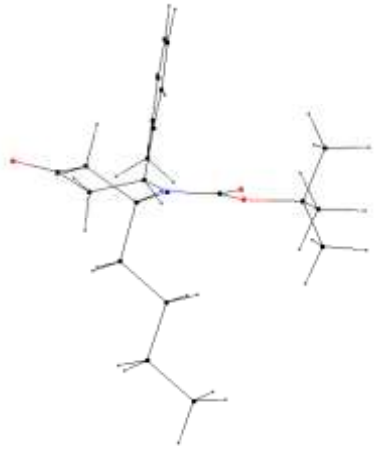
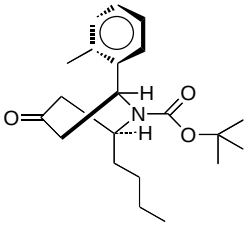
Figure 4.6 50% Probability Thermal Ellipsoids of **51c**.

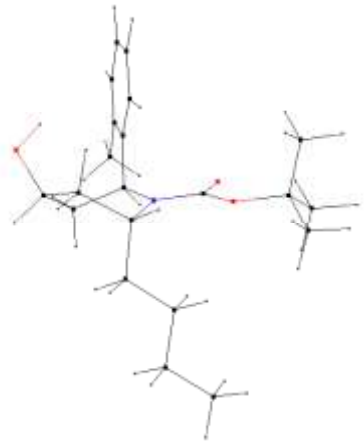
Table 4.10 Crystal Data and Structure Refinement for **51c**.

Empirical formula	$C_{24}H_{29}NO_3$	
Formula weight	379.48	
Temperature	193 K	
Wavelength	0.71073	
Crystal system	Monoclinic	
SG	P2(1)/c	
Unit cell dimensions	a = 9.797 (2) Å	α = 90 °
	b = 6.1428 (12) Å	β = 93.51 (3)°
	c = 35.557 (7) Å	γ = 90°
Volume	2135.9 (7) $Å^3$	
Z, calculated density	4, 1.180 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F (000)	816	
Crystal size	0.40 x 0.22 x 0.18 mm	
Theta range for data	2.08 to 25.05 deg	
Index ranges	-11<=h<=11, -6<=k<=7, -42<=l<=42	
Reflns col./unique	14663 / 3789 [R(int) = 0.0656]	
Completeness	99.8 %	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3789 / 0 / 253	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma (I)]	R1 = 0.0876, wR2 = 0.2368	
R indices (all data)	R1 = 0.1263, wR2 = 0.2940	
Largest diff. peak and hole	0.442 and -0.319 $e.A^{-3}$	

CIF file of compound **51c** is reported in the appendix A.

Table 4.11 *Ab initio* Minimized Geometries for Twist-Boat Conformations.[28]

 **52a-TBAr$_{ax}$**	
 **52a-TBR$_{ax}$** (enantiomer)	
 **51a-TB$_{diax}$**	



65-TB$_{diax}$

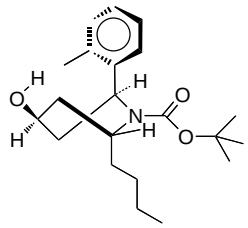


Table 4.12 Coordinates of All Stationary Points.[28]

(*E*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (**51a-CR$_{ax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.482212	-1.084056	2.446789
2	6	0	-0.903240	-0.668916	1.960232
3	6	0	-0.926649	-0.765860	0.409316
4	1	0	-1.116670	0.368719	2.241532
5	1	0	-1.633555	-1.310578	2.451096
6	6	0	1.680429	-0.491091	1.700036
7	6	0	1.489874	-0.375523	0.161690
8	1	0	2.569470	-1.070373	1.966342
9	1	0	1.825279	0.524742	2.097453
10	7	0	0.122503	0.153450	-0.099210
11	6	0	-0.074706	1.518705	0.096946
12	8	0	1.034989	2.223233	-0.228675
13	6	0	1.056394	3.696180	-0.146191
14	6	0	2.480951	4.027626	-0.598831
15	1	0	3.217368	3.569104	0.069407
16	1	0	2.634876	5.111665	-0.590230
17	1	0	2.659402	3.660273	-1.614568
18	6	0	0.827189	4.149929	1.299199
19	1	0	1.552888	3.673685	1.968395
20	1	0	-0.180815	3.904471	1.635866
21	1	0	0.967264	5.234494	1.368420
22	6	0	0.028565	4.289834	-1.114906
23	1	0	0.196899	3.907924	-2.127969
24	1	0	0.137780	5.379891	-1.141291

25	1	0	-0.989273	4.046185	-0.807681
26	8	0	-1.122557	2.011721	0.483040
27	6	0	-2.289499	-0.716776	-0.288630
28	1	0	-0.542894	-1.759872	0.158642
29	6	0	-3.254780	-1.714849	-0.007925
30	6	0	-2.566631	0.210121	-1.301869
31	6	0	-4.473770	-1.691627	-0.700258
32	6	0	-4.752727	-0.735206	-1.672193
33	6	0	-3.781548	0.211977	-1.984128
34	1	0	-1.822877	0.945489	-1.572534
35	6	0	-3.039890	-2.844738	0.979950
36	1	0	-2.009251	-3.216164	0.988470
37	1	0	-3.687865	-3.690133	0.727808
38	1	0	-3.283832	-2.552920	2.009187
39	1	0	-5.211496	-2.459020	-0.475894
40	1	0	-5.707087	-0.745510	-2.192015
41	1	0	-3.960627	0.953167	-2.758479
42	1	0	2.180123	0.376276	-0.216697
43	6	0	1.778447	-1.683023	-0.600832
44	6	0	3.281403	-1.929802	-0.802773
45	1	0	1.285103	-1.624777	-1.579532
46	1	0	1.350185	-2.549485	-0.079069
47	6	0	3.580264	-3.238673	-1.545442
48	1	0	3.792718	-1.946021	0.170286
49	1	0	3.714599	-1.087557	-1.361829
50	6	0	5.078279	-3.479935	-1.757046
51	1	0	3.068454	-3.227319	-2.517952
52	1	0	3.149532	-4.079622	-0.984079
53	1	0	5.531016	-2.673318	-2.346721
54	1	0	5.259516	-4.421696	-2.287020
55	1	0	5.610905	-3.528738	-0.799362
56	8	0	0.635311	-1.846570	3.382594

(*E*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (**51a-CAr$_{ax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.533188	-2.853972	-0.170723
2	6	0	-1.046919	-2.090735	1.040470
3	6	0	-1.235419	-0.573467	0.815162
4	1	0	-0.314388	-2.243435	1.846287
5	1	0	-1.977513	-2.558188	1.369071
6	6	0	0.293198	-2.038980	-1.151629
7	6	0	0.978858	-0.817669	-0.515542
8	1	0	-0.393944	-1.711302	-1.942725
9	1	0	1.023568	-2.698009	-1.628846
10	7	0	-0.021562	0.003430	0.207157
11	6	0	0.177343	1.343944	0.449454
12	8	0	1.313628	1.788495	-0.145011

13	6	0	1.697421	3.208906	-0.074613
14	6	0	2.992070	3.242131	-0.891583
15	1	0	3.748591	2.586887	-0.447330
16	1	0	3.391613	4.261201	-0.920841
17	1	0	2.810030	2.912697	-1.919876
18	6	0	1.963278	3.611673	1.379754
19	1	0	2.711405	2.948145	1.828039
20	1	0	1.048189	3.565215	1.971286
21	1	0	2.355557	4.634473	1.411271
22	6	0	0.620430	4.078427	-0.732404
23	1	0	0.426956	3.735719	-1.755045
24	1	0	0.968079	5.116469	-0.783041
25	1	0	-0.311568	4.045532	-0.166593
26	8	0	-0.586268	2.026234	1.116803
27	1	0	-1.330729	-0.106620	1.798308
28	6	0	-2.521215	-0.253221	0.041258
29	6	0	2.176090	-1.200511	0.386723
30	1	0	1.366814	-0.191733	-1.323070
31	6	0	3.404152	-1.703420	-0.385159
32	1	0	1.867662	-1.958638	1.120096
33	1	0	2.460526	-0.309690	0.957838
34	6	0	4.597956	-2.013765	0.528298
35	1	0	3.701202	-0.943330	-1.123031
36	1	0	3.154186	-2.606792	-0.958907
37	6	0	5.832060	-2.500894	-0.237607
38	1	0	4.301291	-2.773359	1.265167
39	1	0	4.855023	-1.114099	1.105169
40	1	0	5.615754	-3.420405	-0.795184
41	1	0	6.665263	-2.712380	0.442001
42	1	0	6.173770	-1.748982	-0.959613
43	6	0	-2.488119	0.073066	-1.317999
44	6	0	-3.655566	0.327402	-2.038352
45	1	0	-1.528375	0.160077	-1.816990
46	6	0	-3.768020	-0.279971	0.707633
47	6	0	-4.930429	-0.024194	-0.029677
48	6	0	-4.887302	0.268134	-1.392576
49	1	0	-3.596832	0.576825	-3.094495
50	1	0	-5.889219	-0.043461	0.483655
51	1	0	-5.807352	0.462816	-1.937106
52	6	0	-3.884707	-0.528644	2.196428
53	1	0	-3.528946	-1.522488	2.493627
54	1	0	-4.927570	-0.448625	2.517363
55	1	0	-3.305895	0.205497	2.771425
56	8	0	-0.761616	-4.035913	-0.334530

(*E*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (**51a-TB$_{diax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.289020	-2.704813	-1.016859
2	6	0	1.365245	-2.239055	0.430600
3	6	0	1.121655	-0.726357	0.636193
4	1	0	2.339082	-2.529017	0.830761
5	1	0	0.611240	-2.809833	0.990550
6	6	0	0.354784	-1.905831	- 1.914163
7	6	0	-0.723262	-1.130953	-1.135648
8	1	0	-0.098756	-2.586566	-2.641773
9	1	0	0.982057	-1.208700	-2.484630
10	7	0	-0.082105	-0.289390	-0.101075
11	6	0	-0.566270	0.947093	0.268325
12	8	0	-1.579654	1.353850	-0.536109
13	1	0	-1.213327	-0.441355	-1.824929
14	6	0	-1.804757	-2.098745	-0.591989
15	6	0	-2.208882	2.673675	-0.348844
16	6	0	-3.259349	2.700349	-1.462717
17	1	0	-2.786208	2.593856	-2.444436
18	1	0	-3.803208	3.650631	-1.442992
19	1	0	-3.982289	1.887402	-1.337312
20	6	0	-1.172228	3.782758	-0.557624
21	1	0	-0.689491	3.672861	-1.535097
22	1	0	-0.407259	3.756024	0.219315
23	1	0	-1.669982	4.758759	-0.532687
24	6	0	-2.876454	2.752378	1.028180
25	1	0	-3.579142	1.922254	1.159653
26	1	0	-3.439119	3.689404	1.109058
27	1	0	-2.133302	2.717501	1.825727
28	8	0	1.920789	-3.659762	-1.421997
29	8	0	-0.107113	1.586362	1.203232
30	1	0	0.913575	-0.565966	1.696750
31	6	0	2.375926	0.088900	0.291178
32	1	0	-1.333826	-2.890592	0.006183
33	1	0	-2.238668	-2.606571	-1.465564
34	6	0	-2.933526	-1.464477	0.227685
35	1	0	-2.510834	-0.947431	1.099422
36	6	0	-3.966272	-2.493067	0.709448
37	1	0	-3.436783	-0.694481	-0.371332
38	1	0	-3.460040	-3.265120	1.306522
39	1	0	-4.395235	-3.013975	-0.158378
40	6	0	-5.093040	-1.867276	1.537537
41	1	0	-4.697369	-1.365158	2.428982
42	1	0	-5.811115	-2.624210	1.872693
43	1	0	-5.645583	-1.119555	0.955080
44	6	0	3.422888	0.193659	1.234869
45	6	0	2.517637	0.717415	-0.949542
46	6	0	3.313521	-0.386633	2.628672
47	6	0	4.582783	0.891934	0.878730

48	6	0	4.723475	1.493383	-0.371572
49	1	0	5.387736	0.973064	1.605784
50	6	0	3.678875	1.412717	-1.288206
51	1	0	1.693702	0.689533	-1.655449
52	1	0	3.759579	1.890289	-2.261114
53	1	0	5.635877	2.029486	-0.618602
54	1	0	2.471380	0.053112	3.178345
55	1	0	4.222892	-0.182408	3.201786
56	1	0	3.166360	-1.473437	2.628693

(*Z*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (**52a -C_{diax}**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.056163	0.087064	2.729735
2	6	0	0.637708	-1.325586	2.357420
3	6	0	0.378674	-1.488808	0.837285
4	1	0	-0.318152	-1.530421	2.859326
5	1	0	1.371028	-2.043814	2.730654
6	6	0	0.146609	1.173021	2.179269
7	6	0	-0.146315	0.999398	0.663552
8	1	0	0.589319	2.148803	2.394548
9	1	0	-0.808819	1.110157	2.719898
10	7	0	-0.533460	-0.405155	0.398155
11	6	0	-1.846817	-0.767241	0.164713
12	8	0	-2.622348	0.306648	-0.114893
13	6	0	-4.055774	0.152145	-0.425660
14	6	0	-4.495059	1.598835	-0.668426
15	1	0	-4.330034	2.209514	0.225360
16	1	0	-5.561098	1.630443	-0.916222
17	1	0	-3.933543	2.040612	-1.498004
18	6	0	-4.796332	-0.443511	0.776073
19	1	0	-4.615414	0.160284	1.672469
20	1	0	-4.476234	-1.468443	0.967494
21	1	0	-5.874348	-0.441136	0.579297
22	6	0	-4.230846	-0.686972	-1.695354
23	1	0	-3.651128	-0.255157	-2.518773
24	1	0	-5.286589	-0.690070	-1.989221
25	1	0	-3.906171	-1.715690	-1.534628
26	8	0	-2.247313	-1.924813	0.186564
27	1	0	-0.206198	-2.401153	0.713496
28	6	0	1.638465	-1.636155	-0.025723
29	1	0	-1.024243	1.596996	0.425844
30	6	0	0.998993	1.499250	-0.242284
31	6	0	2.917131	-1.469153	0.525743
32	6	0	4.072960	-1.650845	-0.235425
33	1	0	3.029202	-1.182058	1.565292
34	6	0	1.528112	-2.013881	-1.386187

35	6	0	2.700069	-2.194050	-2.131598
36	6	0	3.965230	-2.014537	-1.574237
37	1	0	5.047511	-1.510510	0.224185
38	1	0	2.612190	-2.488939	-3.174970
39	1	0	4.854456	-2.165404	-2.180678
40	6	0	0.197949	-2.220026	-2.075711
41	1	0	-0.519625	-2.770560	-1.460465
42	1	0	0.336066	-2.768736	-3.012683
43	1	0	-0.276060	-1.261229	-2.321545
44	8	0	2.029275	0.330610	3.419870
45	1	0	1.962703	1.091648	0.081265
46	6	0	1.087331	3.031481	-0.305869
47	1	0	0.822811	1.107955	-1.251735
48	1	0	1.284266	3.444011	0.693818
49	1	0	0.115230	3.441369	-0.619548
50	6	0	2.176978	3.526019	-1.266851
51	1	0	3.146636	3.112271	-0.957224
52	6	0	2.270504	5.053593	-1.335368
53	1	0	1.981916	3.124438	-2.271145
54	1	0	2.504110	5.481456	-0.352626
55	1	0	1.323988	5.495026	-1.671404
56	1	0	3.053130	5.374605	-2.032073

(*Z*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (52a-**TBAr$_{ax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.289020	-2.704813	-1.016859
2	6	0	1.365245	-2.239055	0.430600
3	6	0	1.121655	-0.726357	0.636193
4	1	0	2.339082	-2.529017	0.830761
5	1	0	0.611240	-2.809833	0.990550
6	6	0	0.354784	-1.905831	-1.914163
7	6	0	-0.723262	-1.130953	-1.135648
8	1	0	-0.098756	-2.586566	-2.641773
9	1	0	0.982057	-1.208700	-2.484630
10	7	0	-0.082105	-0.289390	-0.101075
11	6	0	-0.566270	0.947093	0.268325
12	8	0	-1.579654	1.353850	-0.536109
13	1	0	-1.213327	-0.441355	-1.824929
14	6	0	-1.804757	-2.098745	-0.591989
15	6	0	-2.208882	2.673675	-0.348844
16	6	0	-3.259349	2.700349	-1.462717
17	1	0	-2.786208	2.593856	-2.444436
18	1	0	-3.803208	3.650631	-1.442992
19	1	0	-3.982289	1.887402	-1.337312
20	6	0	-1.172228	3.782758	-0.557624
21	1	0	-0.689491	3.672861	-1.535097
22	1	0	-0.407259	3.756024	0.219315

23	1	0	-1.669982	4.758759	-0.532687
24	6	0	-2.876454	2.752378	1.028180
25	1	0	-3.579142	1.922254	1.159653
26	1	0	-3.439119	3.689404	1.109058
27	1	0	-2.133302	2.717501	1.825727
28	8	0	1.920789	-3.659762	-1.421997
29	8	0	-0.107113	1.586362	1.203232
30	1	0	0.913575	-0.565966	1.696750
31	6	0	2.375926	0.088900	0.291178
32	1	0	-1.333826	-2.890592	0.006183
33	1	0	-2.238668	-2.606571	-1.465564
34	6	0	-2.933526	-1.464477	0.227685
35	1	0	-2.510834	-0.947431	1.099422
36	6	0	-3.966272	-2.493067	0.709448
37	1	0	-3.436783	-0.694481	-0.371332
38	1	0	-3.460040	-3.265120	1.306522
39	1	0	-4.395235	-3.013975	-0.158378
40	6	0	-5.093040	-1.867276	1.537537
41	1	0	-4.697369	-1.365158	2.428982
42	1	0	-5.811115	-2.624210	1.872693
43	1	0	-5.645583	-1.119555	0.955080
44	6	0	3.422888	0.193659	1.234869
45	6	0	2.517637	0.717415	-0.949542
46	6	0	3.313521	-0.386633	2.628672
47	6	0	4.582783	0.891934	0.878730
48	6	0	4.723475	1.493383	-0.371572
49	1	0	5.387736	0.973064	1.605784
50	6	0	3.678875	1.412717	-1.288206
51	1	0	1.693702	0.689533	-1.655449
52	1	0	3.759579	1.890289	-2.261114
53	1	0	5.635877	2.029486	-0.618602
54	1	0	2.471380	0.053112	3.178345
55	1	0	4.222892	-0.182408	3.201786
56	1	0	3.166360	-1.473437	2.628693

(*Z*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (**52a-TBR$_{ax}$**, enantiomers)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.894258	-1.886594	-1.837812
2	6	0	-2.212665	-0.412515	-1.998696
3	6	0	-1.803885	0.420723	-0.771645
4	1	0	-3.273551	-0.296534	-2.235564
5	1	0	-1.651677	-0.052959	-2.874797
6	6	0	-0.689947	-2.180232	-0.954923
7	6	0	0.331492	-1.024185	-0.858041
8	1	0	-0.188870	-3.077928	-1.327879
9	1	0	-1.067203	-2.433394	0.044418

10	7	0	-0.349043	0.246232	-0.511368
11	6	0	0.357055	1.425344	-0.360282
12	8	0	1.677673	1.243298	-0.567600
13	6	0	1.477687	-1.456285	0.064626
14	1	0	0.778738	-0.904946	-1.854882
15	6	0	2.644856	2.331697	-0.328916
16	6	0	3.984967	1.659261	-0.637930
17	1	0	4.145446	0.795883	0.014340
18	1	0	4.803057	2.371703	-0.487347
19	1	0	4.014024	1.315384	-1.677104
20	6	0	2.585451	2.773136	1.136818
21	6	0	2.381934	3.487935	-1.299634
22	1	0	2.383576	3.123116	-2.332938
23	1	0	3.178715	4.234376	-1.203463
24	1	0	1.422741	3.964770	-1.094608
25	8	0	-2.542139	-2.769592	-2.363997
26	8	0	-0.176087	2.491529	-0.081639
27	1	0	-1.920179	1.475995	-1.026721
28	6	0	-2.676993	0.178041	0.476304
29	6	0	1.433757	-1.461775	1.477207
30	6	0	-4.125316	0.663564	0.317759
31	1	0	-2.209408	0.719590	1.306545
32	1	0	-2.678461	-0.885035	0.753864
33	6	0	-4.938604	0.551255	1.614772
34	6	0	-6.384147	1.034767	1.461727
35	6	0	2.543145	-1.966427	2.172615
36	6	0	2.612709	-1.968639	-0.578473
37	6	0	3.667138	-2.470751	1.521028
38	1	0	2.514628	-1.966047	3.259934
39	6	0	3.700137	-2.476886	0.128639
40	1	0	1.623001	3.230304	1.372246
41	1	0	3.378145	3.504549	1.330742
42	1	0	2.746991	1.914510	1.797787
43	6	0	0.268547	-0.940148	2.291015
44	1	0	-4.636558	0.092829	-0.470011
45	1	0	-4.119790	1.712013	-0.015066
46	1	0	-4.439332	1.129768	2.404558
47	1	0	-4.936415	-0.494263	1.954532
48	1	0	-6.419689	2.087677	1.156391
49	1	0	-6.937272	0.942312	2.403238
50	1	0	-6.919439	0.451632	0.702321
51	1	0	0.420674	-1.165477	3.351384
52	1	0	-0.685810	-1.386442	1.995753
53	1	0	0.150152	0.144063	2.194467
54	1	0	4.503807	-2.856309	2.097416
55	1	0	2.646196	-1.958844	-1.665863
56	1	0	4.563159	-2.865518	-0.405181

(*E*) *N*-Boc-2-(1-methylethyl)-6-butyl-4-piperidinone (**53b-TB$_{diax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.285518	-0.340654	-1.809472
2	6	0	-1.2893303	0.121837	-2.845484
3	8	0	-1.613643	0.337867	-3.973259
4	6	0	0.136922	0.300012	-2.384255
5	1	0	0.243025	1.353592	-2.146973
6	1	0	0.789817	0.112477	-3.224956
7	6	0	0.559117	-0.525379	-1.162174
8	1	0	1.440084	-0.042924	-0.767117
9	6	0	0.997295	-1.979649	-1.482539
10	6	0	2.287572	-1.992289	-2.313693
11	1	0	2.693998	-2.997824	-2.354879
12	1	0	3.048267	-1.349612	-1.879805
13	1	0	2.122912	-1.672554	-3.337957
14	6	0	-0.063649	-2.869663	-2.134891
15	1	0	0.342082	-3.863816	-2.295204
16	1	0	-0.379643	-2.496234	-3.104887
17	1	0	-0.938097	-2.981101	-1.504256
18	1	0	1.240337	-2.423569	-0.524955
19	7	0	-0.467841	-0.445351	-0.104176
20	6	0	-1.890718	-0.122366	-0.343568
21	6	0	-2.304282	1.263678	0.190195
22	6	0	-1.667044	2.501391	-0.443954
23	1	0	-0.588524	2.470388	-0.308594
24	6	0	-2.200513	3.799365	0.169333
25	6	0	-1.564234	5.050122	-0.435967
26	1	0	-0.487781	5.053874	-0.287871
27	1	0	-1.962619	5.952054	0.018185
28	1	0	-1.750837	5.108093	-1.504608
29	1	0	-2.025554	3.787362	1.242736
30	1	0	-3.279201	3.843063	0.036187
31	1	0	-1.851445	2.525682	-1.516286
32	1	0	-2.115259	1.275213	1.255874
33	1	0	-3.384956	1.327635	0.074427
34	1	0	-2.460214	-0.830999	0.239792
35	6	0	-0.142899	-0.687770	1.195721
36	8	0	-0.949850	-0.731115	2.083511
37	8	0	1.159226	-0.860840	1.369948
38	6	0	1.751311	-1.116328	2.667599
39	6	0	1.232354	-2.431632	3.243689
40	1	0	1.375751	-3.237699	2.531144
41	1	0	0.184425	-2.369868	3.495427
42	1	0	1.791508	-2.675782	4.141179
43	6	0	1.505158	0.062260	3.606626
44	1	0	1.830103	0.987265	3.140725
45	1	0	2.082194	-0.075472	4.515486
46	1	0	0.461873	0.150662	3.869492
47	6	0	3.237098	-1.229894	2.338597

48	1	0	3.414179	-2.041178	1.641309
49	1	0	3.807446	-1.422699	3.240491
50	1	0	3.600982	-0.310940	1.892733
51	1	0	-3.234108	0.139826	-2.01496
52	1	0	-2.437272	-1.398518	-1.99365

(*E*) *N*-Boc-2-(1-methylethyl)-6-butyl-4-piperidinone (**53b-C^{i}Pr$_{ax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.155256	0.803959	-1.990562
2	6	0	-1.145069	1.224316	-3.021898
3	8	0	-1.414111	1.929600	-3.945583
4	6	0	0.200914	0.584916	-2.826387
5	1	0	0.892320	0.959433	-3.567514
6	1	0	0.070632	-0.480956	-3.002074
7	6	0	0.756103	0.770547	-1.410593
8	6	0	1.398144	2.160522	-1.151968
9	1	0	1.654207	2.172308	-0.097629
10	6	0	0.500249	3.375224	-1.415088
11	1	0	-0.432438	3.326570	-0.864396
12	1	0	0.266944	3.493217	-2.466805
13	1	0	1.010445	4.278178	-1.093963
14	6	0	2.717758	2.304587	-1.921996
15	1	0	3.380360	1.463558	-1.738242
16	1	0	3.235975	3.205560	-1.609401
17	1	0	2.561220	2.381109	-2.993637
18	1	0	1.552297	0.053339	-1.306828
19	7	0	-0.253772	0.388954	-0.394150
20	6	0	-1.686636	0.746736	-0.519970
21	1	0	-1.833635	1.730659	-0.088390
22	6	0	-2.645890	-0.213624	0.222083
23	1	0	-3.644513	0.028712	-0.13692
24	1	0	-2.636337	0.003319	1.277468
25	6	0	-2.395644	-1.710181	0.017232
26	1	0	-2.329752	-1.953850	-1.041335
27	6	0	-3.493031	-2.567371	0.654081
28	1	0	-4.455380	-2.309596	0.216509
29	1	0	-3.564362	-2.328030	1.712476
30	6	0	-3.247744	-4.066720	0.488584
31	1	0	-3.204505	-4.344266	-0.561170
32	1	0	-4.039277	-4.648195	0.951221
33	1	0	-2.308493	-4.363460	0.947179
34	1	0	-1.439792	-1.986247	0.451136
35	6	0	0.205011	0.191668	0.883861
36	8	0	-0.459146	0.335480	1.869591
37	8	0	1.472546	-0.193866	0.905126
38	6	0	2.184717	-0.493165	2.131294
39	6	0	1.534949	-1.674151	2.848355

40	1	0	1.434024	-2.515308	2.169976
41	1	0	0.560482	-1.417814	3.236117
42	1	0	2.166346	-1.984330	3.674735
43	6	0	2.273222	0.744282	3.021379
44	1	0	2.697810	1.577014	2.469430
45	1	0	2.926945	0.534155	3.861861
46	1	0	1.304934	1.033406	3.401169
47	6	0	3.570675	-0.880658	1.623356
48	1	0	3.509137	-1.736055	0.960129
49	1	0	4.217148	-1.137146	2.455373
50	1	0	4.022372	-0.058261	1.079902
51	1	0	-3.020488	1.449772	-2.060866
52	1	0	-2.472620	- 0.187852	-2.302255

(*E*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinol (**65-CAr$_{ax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.472269	-3.079935	-0.406796
2	6	0	-1.207234	-2.514517	0.807982
3	6	0	-1.230600	-0.972805	0.869104
4	1	0	-0.707768	-2.914407	1.700231
5	1	0	-2.241830	-2.876479	0.842511
6	6	0	0.972152	-2.613865	-0.343350
7	6	0	1.182649	-1.085059	-0.229416
8	1	0	1.505747	-2.968694	-1.230324
9	1	0	1.431383	-3.108380	0.522699
10	7	0	0.052418	-0.371530	0.433980
11	6	0	0.066694	1.000791	0.582200
12	8	0	1.035685	1.585797	-0.167024
13	6	0	1.217769	3.046845	-0.161360
14	6	0	2.402997	3.235958	-1.112678
15	1	0	3.292928	2.721976	-0.734338
16	1	0	2.636588	4.300991	-1.214786
17	1	0	2.169485	2.836095	-2.104786
18	6	0	1.570477	3.537078	1.247377
19	1	0	2.449846	3.005632	1.628695
20	1	0	0.738149	3.383423	1.935106
21	1	0	1.810086	4.606076	1.213692
22	6	0	-0.034564	3.732837	-0.718675
23	1	0	-0.278455	3.330660	-1.708100
24	1	0	0.152527	4.807612	-0.824750
25	1	0	-0.889800	3.584496	-0.058461
26	8	0	-0.733302	1.605372	1.282448
27	1	0	-1.358198	-0.690917	1.916448
28	6	0	-2.445757	-0.408621	0.111931
29	1	0	-0.486857	-4.180639	-0.336966
30	8	0	-1.005372	-2.676643	-1.665101
31	6	0	2.510575	-0.835564	0.526734

32	1	0	1.274114	-0.672642	-1.240751
33	6	0	3.754572	-1.336305	-0.221472
34	1	0	2.443913	-1.324669	1.509439
35	1	0	2.628454	0.233615	0.711459
36	6	0	5.061813	-0.993872	0.506800
37	1	0	3.775144	-0.890486	-1.227262
38	1	0	3.706631	-2.423715	-0.369939
39	6	0	6.311060	-1.484507	-0.231891
40	1	0	5.038477	-1.429028	1.516058
41	1	0	5.122676	0.094602	0.647693
42	1	0	6.296607	-2.574499	-0.355256
43	1	0	7.226048	-1.223577	0.312135
44	1	0	6.380211	-1.040252	-1.232519
45	6	0	-2.357965	-0.035357	-1.234445
46	6	0	-3.471231	0.433020	-1.933209
47	1	0	-1.403567	-0.117840	-1.742907
48	6	0	-3.684703	-0.283261	0.778064
49	6	0	-4.793327	0.184541	0.060627
50	6	0	-4.699790	0.538864	-1.284368
51	1	0	-3.373590	0.714263	-2.978656
52	1	0	-5.746340	0.282493	0.576076
53	1	0	-5.576387	0.901136	-1.815060
54	6	0	-3.841862	-0.603307	2.249124
55	1	0	-3.574574	-1.639785	2.490222
56	1	0	-4.877486	-0.450546	2.568264
57	1	0	-3.205444	0.046665	2.863107
58	1	0	-1.970480	-2.616446	-1.593108

(*E*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinol (**65-CR$_{ax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.485085	-1.230498	2.375887
2	6	0	-0.887689	-0.708462	1.915474
3	6	0	-0.942101	-0.782744	0.369830
4	1	0	-1.035949	0.332351	2.225660
5	1	0	-1.666614	-1.302556	2.395186
6	6	0	1.650979	-0.521404	1.659293
7	6	0	1.480315	-0.404448	0.123216
8	1	0	2.590983	-1.024286	1.914842
9	1	0	1.723176	0.499344	2.064226
10	7	0	0.113038	0.129115	-0.149743
11	6	0	-0.076552	1.494174	0.041016
12	8	0	1.033758	2.194106	-0.302722
13	6	0	1.061675	3.664635	-0.226862
14	6	0	2.482921	3.989694	-0.695300
15	1	0	3.224221	3.530114	-0.033167
16	1	0	2.641521	5.073181	-0.692545

17	1	0	2.649507	3.617539	-1.711333
18	6	0	0.849407	4.127397	1.218639
19	1	0	1.581472	3.652195	1.881760
20	1	0	-0.155612	3.884956	1.566188
21	1	0	0.992669	5.212037	1.281250
22	6	0	0.026846	4.260480	-1.187268
23	1	0	0.182283	3.872327	-2.200048
24	1	0	0.141539	5.349889	-1.220463
25	1	0	-0.988653	4.022871	-0.867960
26	8	0	-1.117082	1.999191	0.432574
27	6	0	-2.308371	-0.717781	-0.321170
28	1	0	-0.569250	-1.778229	0.103353
29	6	0	-3.282621	-1.707454	-0.039494
30	6	0	-2.583599	0.211685	-1.332895
31	6	0	-4.505500	-1.671601	-0.724446
32	6	0	-4.781678	-0.710497	-1.692500
33	6	0	-3.802357	0.226850	-2.008268
34	1	0	-1.834496	0.939642	-1.608129
35	6	0	-3.072419	-2.846072	0.939647
36	1	0	-2.045749	-3.229010	0.933178
37	1	0	-3.732175	-3.682518	0.687636
38	1	0	-3.302210	-2.559175	1.973397
39	1	0	-5.248709	-2.433205	-0.497891
40	1	0	-5.739199	-0.710411	-2.206699
41	1	0	-3.977940	0.970897	-2.780807
42	8	0	0.638161	-1.163429	3.792072
43	1	0	0.531458	-2.305617	2.159344
44	1	0	0.562103	-0.228765	4.044843
45	1	0	2.173177	0.351778	-0.242430
46	6	0	1.777732	-1.696916	-0.663334
47	6	0	3.283049	-1.943831	-0.847259
48	1	0	1.301112	-1.612534	-1.648470
49	1	0	1.337747	-2.576171	-0.175314
50	6	0	3.591688	-3.234018	-1.618091
51	1	0	3.778686	-1.985776	0.133171
52	1	0	3.727900	-1.089150	-1.377559
53	6	0	5.092348	-3.473543	-1.812575
54	1	0	3.095185	-3.197268	-2.597900
55	1	0	3.150674	-4.088485	-1.085537
56	1	0	5.555585	-2.653185	-2.374480
57	1	0	5.280413	-4.402007	-2.363386
58	1	0	5.610237	-3.547405	-0.848348

(*E*) *N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinol (**65-TB$_{diax}$**)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.371953	-2.672129	-1.018650
2	6	0	1.297351	-2.232257	0.456824
3	6	0	1.063854	-0.721605	0.669254
4	1	0	2.230329	-2.531865	0.942503
5	1	0	0.491936	-2.777100	0.962147
6	6	0	0.381348	-1.874750	-1.907593
7	6	0	-0.735727	-1.152551	-1.133241
8	1	0	-0.069097	-2.533490	-2.658596
9	1	0	0.960702	-1.132961	-2.466930
10	7	0	-0.132379	-0.295013	-0.085367
11	6	0	-0.638902	0.932301	0.274873
12	8	0	-1.660461	1.316919	-0.532304
13	1	0	-1.234270	-0.469430	-1.823615
14	6	0	-1.808781	-2.144954	-0.616554
15	6	0	-2.319586	2.620276	-0.345912
16	6	0	-3.371090	2.621927	-1.459361
17	1	0	-2.895882	2.525796	-2.441171
18	1	0	-3.937535	3.558998	-1.440016
19	1	0	-4.074045	1.791762	-1.333262
20	6	0	-1.310792	3.754900	-0.555669
21	1	0	-0.824736	3.655138	-1.532654
22	1	0	-0.546160	3.747928	0.222006
23	1	0	-1.832338	4.718537	-0.532954
24	6	0	-2.988940	2.684755	1.031193
25	1	0	-3.671182	1.837826	1.163181
26	1	0	-3.573842	3.608137	1.111856
27	1	0	-2.244612	2.667587	1.828216
28	8	0	-0.192670	1.587943	1.206063
29	1	0	0.838781	-0.563177	1.727356
30	6	0	2.316738	0.109517	0.350196
31	1	0	-1.337855	-2.941881	-0.027041
32	1	0	-2.226455	-2.640396	-1.505297
33	6	0	-2.955268	-1.539155	0.200275
34	1	0	-2.547854	-1.028650	1.083167
35	6	0	-3.978420	-2.588296	0.657104
36	1	0	-3.463469	-0.767309	-0.392167
37	1	0	-3.467434	-3.361651	1.248582
38	1	0	-4.391067	-3.103115	-0.222382
39	6	0	-5.122946	-1.991098	1.482065
40	1	0	-4.744043	-1.496850	2.385097
41	1	0	-5.834110	-2.762786	1.798148
42	1	0	-5.679609	-1.242344	0.904813
43	6	0	3.351415	0.215417	1.308667
44	6	0	2.468240	0.761234	-0.879749
45	6	0	3.229547	-0.381044	2.694103
46	6	0	4.507878	0.931189	0.976501
47	6	0	4.660232	1.550389	-0.263964

48	1	0	5.302170	1.011090	1.715295
49	6	0	3.628085	1.472428	-1.194901
50	1	0	1.650319	0.738563	-1.592658
51	1	0	3.714247	1.967004	-2.158795
52	1	0	5.570418	2.098580	-0.491532
53	1	0	2.379523	0.050215	3.238230
54	1	0	4.131979	-0.180615	3.279409
55	1	0	3.083904	-1.467372	2.677994
56	8	0	2.698823	-2.607982	-1.537716
57	1	0	1.127201	-3.738296	-1.059643
58	1	0	2.998081	-1.686790	-1.452836

4.6 Experimental

Some of the experimental procedure and IR, GC/MS and NMR data used for the dissertation was recently published and reported with the permission from American Chemical Society.[28]

General. NMR spectra were recorded as $CDCl_3$ or C_6D_6 solutions on a 500 MHz NMR instrument. The ^1H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0.00) or $CHCl_3$ (δ = 7.28) or C_6H_6 (δ = 7.16) as internal standard. The ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to the $CDCl_3$ signal (triplet, centerline δ = 77.0 ppm) or C_6D_6 signal (multiplet, centerline δ = 128.4 ppm). Infrared (IR) spectra were recorded as neat samples (liquid films on NaCl plates). Gas chromatography-mass spectrometry measurements were performed on a GC coupled to a quadruple detector at 70 eV. Analytical thin layer chromatography (TLC) was performed on silica gel plates, 200 μ mesh with F_{254} indicator. Visualization was accomplished by UV light (254 nm), and/or a 10 % ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 230-400 mess silica. The yields are of materials isolated by column chromatography.

Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. TMSCl was distilled from CaH_2 under a positive N_2 atmosphere. ^{n}BuLi (2.5 M in hexane) was commercially available and titrated using sec-butyl alcohol and 1,10-phenanthroline monohydrate in THF. ^{n}BuMgCl (1.6 M in THF), EtMgCl (1. 0 M in THF), MeMgCl (3.0 M in Et_2O), ^{i}PrMgBr (2.0 M in Et_2O), and PhMgCl (2.80 M in Et_2O) were commercially available and titrated using menthol and 1,10-phenanthroline monohydrate in THF.[38] All glassware was flamed-dried under high vacuum and purged with argon and then cooled under a dry nitrogen atmosphere. Low temperature baths (as low as -78 ^{o}C) were prepared using thermoflasks with dry ice-*iso*propyl alcohol slush bath mixtures. All reactions were

conducted under a positive, dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

Method A: Synthesis of Grignard reagents from heteroaryl compounds. The heteroaryl Grignard reagents were prepared from a slight modification of a literature procedure.To the heteroaryl compound (2.0 mmol) in THF (3.0 mL) at 0 ^{o}C under argon, was added ^{n}BuLi (0.80 mL, 2.50 M in hexane, 2.00 mmol) dropwise. Then the reaction mixture was warmed to room temperature and stirred for 2 hours at this temperature. The reaction mixture was transferred to flame-dried $MgBr_2$ (368 mg, 2.0 mmol) in THF (5.0 mL) at 0 ^{o}C via cannula under argon, stirred for 30 min at this temperature and used for further reactions using General Procedure **A**.

Method B: Synthesis of Grignard reagents from aryl halides. Aryl Grignard reagents that were not available commercially were synthesized in situ by using a modified literature procedure[39] from the corresponding aryl halides as described below. To magnesium (192 mg) in THF (5.0 mL) under argon, was added a catalytic amount of iodide (15 mg). Then a solution of aryl halide (2.00 mmol in 5.0 mL THF) was added dropwise. During addition, the reaction mixture was heated at 50 ^{o}C for 10 minutes. After the addition was complete, the reaction mixture was stirred for an additional 30 minutes at room temperature and used for the conjugate addition reactions using General Procedure A.

Method C: Synthesis of Grignard reagent via halogen metal exchange. The halogen metal exchange reaction of the vinyl iodide was performed by using the literature procedure.[40] To ^{i}PrMgCl (1.20 mL, 2.0 M in Et_2O, 2.4 mmol) in THF (3.0 mL) at 0 ^{o}C was added ^{n}BuLi (1.92 mL, 2.5 M in hexane, 4.8 mmol) under argon and the mixture was stirred for 10 minutes. Iodocompound (2.0 mmol) was added and the mixture was stirred for 1 hour at 0 ^{o}C and then used for further reactions following General Procedure A.

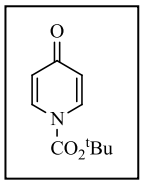
General Procedure A: Reaction of Grignard reagents with *N*-carbamoyl-4-pyridones in the presence of TMSCl. To the cooled -78 ^{o}C solution of Grignard reagent (1-2 equiv) was added the starting *N*-carbamoyl-4-pyridone (**1** or **2**) [1.0 mmol mixed with TMSCl (3.0 equiv) in THF (3.0 mL)] dropwise. The reaction mixture was allowed to warm to room temperature over night with stirring. Then the reaction mixture was diluted with dichloromethane (5.0 mL), quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with dichloromethane (3×10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 1-3 % MeOH in CH_2Cl_2, v/v) to give pure compounds.

General Procedure B: Reaction of organocuprate reagents with *N*-Boc-2-alkyl-2,3-dihydropyridone. The organocuprate reagents used for the reaction were prepared by the reaction of either RLi (2.0 equiv), CuCN (1.0 equiv) and LiCl (2.0 equiv) or the reaction of RMgX (1.0 equiv) with CuI (1.0 equiv). In the first method, to the mixture of LiCl (2.0 equiv), CuCN (1.0 equiv) and Me_2S (2.0 equiv) under argon in diethyl ether was added ^{n}BuLi (2.0 equiv) at -78 ^{o}C and the reaction mixture warmed up to -30 ^{o}C over 30 minutes. In the second method, CuI (1.0 equiv) was mixed with RMgX (1.0 equiv) in THF under argon at -60 ^{o}C and the resulting mixture was warmed to -30 ^{o}C over 30 minutes following slight modification of Comin's procedure.[21] The reaction mixture was cooled to -78 ^{o}C, boron trifluoride etherate (0.5 equiv) was added and the resulting mixture was stirred for 10 minutes before adding *N*-carbamoyl-4-pyridone (1.0 equiv in 2.0 mL diethyl ether) over 10 minutes at -78 ^{o}C. The reaction mixture was warmed to room temperature over night with continuous stirring. Then the reaction mixture was diluted with dichloromethane (5.0 mL), quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with dichloromethane (3×10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered,

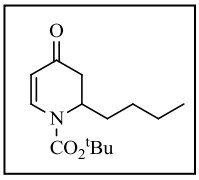
concentrated in vacuo, and purified by flash column chromatography (silica, 1-3 % MeOH in CH_2Cl_2, v/v) to give pure compounds.

General Procedure C: Preparation of *N*-carbamoyl-4-pyridones (1-2). *N*-Carbamoyl-4-pyridones (**1-2**) used for the reactions were prepared using a modified literature procedure.[41] To the solution of 4-hydroxypyridine (1.90 g, 20.0 mmol) in ^{t}BuOH (20.0 mL) was added sodium hydride (624 mg, 26.0 mmol) under argon and the reaction mixture was heated in hot water bath (~50 ^{o}C) until the mixture turned to a slurry. Then the appropriate chloroformate (26.0 mmol) in ^{t}BuOH (7.0 mL) was added dropwise. The reaction mixture was cooled to room temperature and stirred for 12 hours at that temperature. The reaction mixture was quenched with water (20.0 mL) with caution, acidified to pH = 7 with 10% HCl and the aqueous portion was extracted with ether (3 x 15.0 mL). The ether layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated by vacuum to give crude product. Purification by flash chromatography (1-3% MeOH in CH_2Cl_2, v/v) afforded *N*-carbamoyl-4-pyridones **23**.

Preparation of *N*-tert-butoxycarbonyl-4-pyridone (23). Employing general procedure C and using, *tert*-butoxycarbonyl anhydride (5.67 g, 26.0 mmol), 4-hydroxypyridine (1.90 g, 20.0 mmol) gave **23** after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) as a white solid in good yields (73%). ^{1}H NMR and ^{13}C NMR data are identical to a literature report.[1]

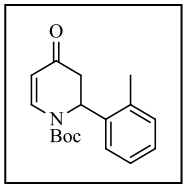


2-*n*-Butyl-2,3-dihydro-*N*-Boc-4-pyridone (24d). Employing general procedure B, ^{n}BuLi (2.00 mmol, 0.80 mLof 2.50 M), *N*-Boc-4-pyridone **23** (195 mg, 1.00 mmol) gave, after purification by flash column chromatography (silica, 2% MeOH:CH_2Cl_2, v/v), **24d** (178 mg, 70%): IR (neat) 2960 (m), 2926 (m), 2862 (w), 1718 (s), 1672 (s), 1597 (s), 1331 (s), 1154 (s), 764 (m) cm^{-1}; ^{1}H NMR δ 0.90 (t, J = 7.20 Hz, 3H), 1.18-

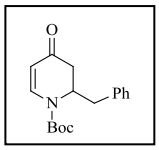


1.36 (m, 4 H), 1.46-1.52 (m, 1H), 1.55 (s, 9H), 1.58-1.69 (m, 2H), 2.44 (dd, *J* = 1.20, 16.50 Hz, 1H), 2.80 (dd, *J* = 6.60, 16.50 Hz, 1H), 4.46-4.60 (m, 1H), 5.28 (d, *J* = 8.10 Hz, 1H), 7.74 (d, *J* = 7.80Hz, 1H); ^{13}C NMR δ 13.9, 22.4, 28.0, 28.1, 30.0, 39.7, 52.9, 83.2, 106.0, 141.1, 151.3, 193.4; mass spectrum m/z (relative intensity) EI 253 (M^+, 4), 197 (13), 153 (24), 140 (8), 96 (99), 57 (100).

***N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone (24j).**[42] Employing method B, general procedure A and using 2-bromotoluene (342 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave white amorphous solid **24j** (273 mg, 95 %): m.p. 117.1-119.5 ^{o}C; IR (neat) 3077 (w), 2974 (m), 2929 (w), 1724 (s), 1667 (s), 1605 (s), 1458 (w), 1417 (m), 1368 (m), 1319 (s), 1258 (m), 1213 (m), 1148 (s), 1009 (w), 976 (w), 923 (w), 853 (w), 756 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 9 H), 2.28 (s, 3 H), 2.48 (d, *J* = 16.5 Hz, 1H), 3.07 (dd, *J* = 8.7, 16.4 Hz, 1H), 5.33 (d, *J* = 8.7 Hz, 1 H), 5.67 (d, *J* = 8.7 Hz, 1H), 6.96-7.12 (m, 4H), 8.08 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 27.9, 40.8, 53.3, 83.7, 106.3, 123.9, 126.6, 127.8, 131.2, 133.8, 137.7, 144.3, 151.4, 191.8; mass spectrum *m/z* (relative intensity) EI 287 (M^+, 0.02), 239 (0.10), 207 (0.42), 187 (56), 172 (6), 158 (7), 144 (29), 130 (100), 117 (100), 96 (51), 70 (36), 51 (13).

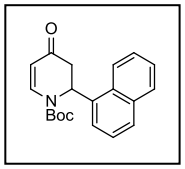


2-Benzyl-2,3-dihydro-*N*-(*tert*-butoxycarbonyl)-4-pyridone (24n). Employing method **B**, general procedure **A** and using benzyl bromide (343 mg, 2.00 mmol), magnesium (192 mg, 8 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column



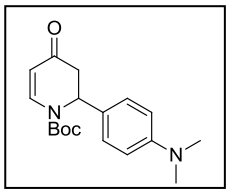
chromatography (silica, 1-3 % methanol:dichloromethane, v/v) gave **24n** (234 mg, 81 %) reported earlier in the literature.[43]

***N*-Boc-2-(1-napthanyl)-2,3-dihydro-4-pyridone (24o)**. Employing method B, general procedure



A and using 1-napthanyl bromide (414 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave white amorphous solid **24o** (256 mg, 79 %): m.p. 126.5-128.3 ^oC; IR (neat) 2977 (w), 1727 (s), 1670 (s), 1312 (b), 1149 (b), 857 (b), 773 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (br s, 9H), 2.87 (d, J = 16.5 Hz, 1H), 3.30 (dd, J = 8.7, 16.5 Hz, 1H), 5.43 (d, J = 8.7 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 7.27–7.92 (m, 7H), 8.25 (d, J = 8.7 Hz,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 41.3, 53.0, 83.7, 106.1, 121.6, 121.9, 125.1, 125.7, 126.6, 128.5, 129.4, 133.9, 134.4, 143.9, 151.3, 191.6; mass spectrum *m/z*, (relative intensity) EI 323 (0.01, M^+), 289 (9), 288 (39), 230 (14), 229 (70), 198 (58), 197 (32), 181 (47), 170 (34), 157 (97), 165 (27), 159 (15), 158 (15), 157(97), 155 (39), 154 (32), 141 (19), 132 (17), 129 (97), 128 (63), 127 (38), 117 (19), 91 (60), 90 (24), 75 (100), 73 (68), 58 (7); HRMS (ESI) calculated for $[C_{20}H_{22}NO_3]^+$: 324.1600, found 324.1606.

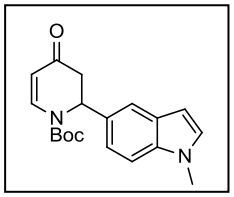
***N*-Boc-2-(4-*N*,*N*-dimethylaminophenyl)-2,3-dihydro-4-pyridone (24p).** Employing method B, general procedure **A** and using *N*,*N*-dimethyl-4-bromoaniline (400 mg, 2.0 mmol), magnesium



(192 mg, 8.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave white amorphous powder **24p**, 302 mg, 96 %: m.p. 115.9-117.3 ^oC; IR (neat) 2976 (w), 2360 (b), 1722 (s), 1656 (s), 1603 (s), 1330 (b), 1221 (s), 1151(s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.78

(d, J = 16.4 Hz, 1H), 2.94 (s, 6H), 3.09 (dd, J = 7.3, 16.5 Hz, 1H), 5.34 (d, J = 8.2 Hz, 1H), 5.61(d, J = 6.9 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 40.5, 41.6, 54.9, 83.4, 106.7, 112.6, 126.9, 127.1, 142.7, 149.8, 151.5, 192.9; mass spectrum *m/z* (relative intensity) EI 317 (M^+ +1, 3.6), 316 (M^+, 18), 260 (30), 216 (41), 147 (100), 146 (37), 134 (20), 91 (5), 77 (11), 57 (32); HRMS (ESI) calculated for $[C_{18}H_{24}N_2O_3]^+$: 316.17786, found 316.17870.

***N*-Boc-2-(5-(1-methyl)-indole)-2,3-dihydro-4-pyridone (24q).** Employing method C, general procedure A and using ^{i}PrMgBr (0.6 mL, 1.2 mmol, 2.0 M in Et_2O), ^{n}BuLi (0.96 mL, 2.50 M in hexane, 2.4 mmol), 5-iodo-*N*-methyl indole (257 mg, 1.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) gave white amorphous solid **24q** (286 mg, 88 %): m.p. 127.4-129.1 ^{o}C; IR (neat) 2977 (w), 1722 (s), 1668 (s), 1604 (s), 1332 (m), 1153 (s), 762 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.87 (d, J = 16.9 Hz, 1H), 3.20 (dd, J = 7.3, 16.5 Hz, 1H), 3.78 (s, 3H), 5.38 (d, J = 8.7 Hz, 1H), 5.79 (d, J = 7.3 Hz, 1H), 6.43 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 3.2 Hz, 1H) 7.13 (dd, J = 1.3, 8.7 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.47 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 32.9, 42.4, 56.1, 83.5, 101.3, 107, 109.6, 118.3, 120.0, 128.5, 129.5, 130.1, 136.3, 143.1, 151.7, 192.9; mass spectrum *m/z* (relative intensity) EI 327 (0.01, M^+), 227 (12), 226 (75), 225 (24), 209 (32), 198 (10), 197 (13), 183 (10), 181 (15), 157 (100), 156 (26), 144 (8), 131(16), 115 (18), 103 (5), 96 (10), 77 (9), 63 (4); Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58 %. Found: C, 69.87; H, 6.90; N, 8.38 %.

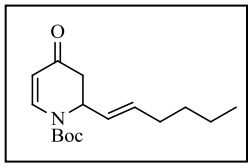


***N*-Boc-2-(2-chloromethylphenyl)-2,3-dihydro-4-pyridone (24r).** Employing method C, general procedure A and using ^{i}PrMgBr (0.6 mL, 1.2 mmol, 2.0 M in diethyl ether), ^{n}BuLi (0.96 mL, 2.4 mmol, 2.50 M in hexane), 2-iodo-(1-chloromethyl)-benzene (253 mg, 1.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **24r** (278 mg, 86 %): IR (neat) 2976 (w), 1725 (s), 1668 (s), 1609 (s), 1370 (s), 1319 (b), 1217 (s), 1150 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (br s, 9H), 2.71 (d, J =16.5 Hz, 1H), 3.31 (dd, J =8.7, 16.5 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.83 (d, J =11.9, 1H), 5.40 (d, J = 8.7 Hz, 1H), 5.84 (d, J = 8.75 Hz, 1H), 7.22-7.32 (m, 4H), 8.09 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 41.9, 43.6, 52.3, 84.0, 106.1, 125.2, 128.4, 129.7, 131.2, 133.5, 139.5, 144.2, 151.2, 191.5; mass spectrum *m/z* (relative intensity) EI 322 (M^+, 2.11), 308 (2), 294 (2), 192 (11), 190 (27), 165 (21), 164 (83), 149 (100), 134 (6), 121 (14), 104 (8), 91 (9), 77 (9), 65 (8), 51 (8); HRMS (ESI) calculated for $[C_{17}H_{21}NO_3Cl]^+$: 322.1210, found 322.1205.

***N*-Boc-2-ethenyl-2,3-dihydro-4-pyridone (24s).**[44] Using general procedure A and vinyl magnesium bromide (1.2 mL, 1.0 M in THF, 1.20 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave yellow oil **24s** (166 mg, 75 %): IR (neat) 2980 (w), 2354 (b), 1723 (s), 1670 (s), 1420 (w), 1335 (w), 1156 (s), 766 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 9H), 2.52 (d, J = 16.5 Hz, 1H), 2.91 (dd, J = 7.3, 16.5 Hz, 1H), 4.05 (br s, 1H), 5.13 (dd, J = 1.3, 16.9 Hz), 5.21 (dd, J = 0.9, 10.5 Hz, 1H), 5.28 (d, J = 8.2 Hz, 1H), 5.79 (ddd, J = 1.4, 6.4,11.9 Hz, 1H), 7.78 (d, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 39.8, 54.4, 83.5, 106.4, 117.0,

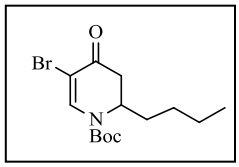
133.0, 142.1, 151.1, 192.4; mass spectrum *m/z* (relative intensity), EI 223 (3.2, M^+), 167 (10), 123 (15), 106 (3), 96 (23), 95 (15), 80 (9), 68 (9), 57 (100), 54 (16).

***N*-Boc-2-(1-hexenyl)-2,3-dihydro-4-pyridone (24t).** Employing method C, general procedure A and using ^{i}PrMgBr (1.20 mL, 2.4 mmol, 2.0 M in diethyl ether), ^{n}BuLi (1.92 mL, 4.8 mmol, 2.50



M in hexane), 1-iodohexene (420 mg, 2.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **23** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **24t** (226 mg, 82 %): IR (neat) 2979 (w), 2354 (b), 1722 (s), 1672 (s), 1335 (b), 1155 (b), 861 (s), 766 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.22-1.34 (m, 4H), 1.53 (s, 9H), 1.99 (q, J = 6.8 Hz, 2H), 2.47 (d, J = 16.0 Hz, 1H), 2.88 (dd, J = 6.8, 16.5 Hz, 1H), 4.98 (br s, 1H), 5.27 (d, J = 8.2 Hz, 1H), 5.45 (dd, J = 5.9, 15.1 Hz, 1H), 5.55-5.61 (m, 1H), 7.76 (d, J = 7.7 Hz,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.0, 27.9, 31.0, 31.7, 40.5, 54.3, 83.2, 106.2, 124.5, 134.0, 142.1, 151.2, 192.9; mass spectrum *m/z* (relative intensity) EI 279 (0.2, M^+), 224 (2), 223 (3), 206 (2), 179 (10), 178 (5), 136 (23), 122 (16), 108 (7), 96 (26), 95 (8), 94 (19), 83 (8), 81 (15), 80 (18), 70 (11), 57 (100), 54 (25); HRMS (ESI) calculated for $[C_{16}H_{25}NO_3]^+$: 279.18300, found: 279.18245.

Synthesis of *N*-Boc-2-Butyl 2,3-dihydro-5-bromo-4-pyridone (32). To the mixture of *N*-*tert*-

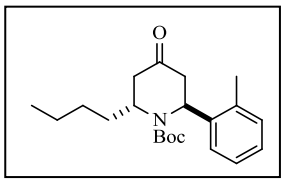


butoxy-carbamoyl-4-pyridone (**23d**, 195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) in THF under argon was added ^{n}BuMgCl (0.75 mL, 1.6 M in THF, 1.2 mmol) dropwise at room temperature and stirred the resulting mixture for 3h. After that tetra-*n*-butyl ammonium fluoride ($^{n}Bu_4NF$, 1.0 M solution in THF, 1.0 mmol) was added and the reaction mixture was stirred the mixture for 10 minutes. Next, *N*-bromosuccinimide (356 mg, 2.0 mmol) was added and the reaction mixture was stirred overnight.

Then the reaction mixture was diluted with dichloromethane (5.0 mL), quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with dichloromethane (3x10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) to give a colorless oil (**32**, 243 mg, 73 %). The use of a literature method[17] (**23d** with NBS in CH_2Cl_2) gave 256 mg, 77 % yield: IR (neat) 3105 (w), 2977 (w), 1733 (s), 1677 (s), 1401 (m), 1363 (m), 1259 (m), 1210 (s), 1116 (w), 776 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 1.16-1.29 (m, 4H), 1.53 (s, 3H), 1.55-1.65 (m, 2H), 2.66 (d, J = 16.5 Hz, 1H), 2.86 (dd, J = 6.7, 16.5 Hz, 1H), 4.52 (br s, 1H), 8.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 22.2, 27.7, 27.8, 30.0, 39.4, 53.4, 84, 99.2, 142.5, 150.1, 185.8; mass spectrum *m/z* (relative intensity) EI 333 (M^+, 0.1), 331 (M^+ 0.1), 233 (28), 231 (29), 176 (98), 174 (100), 152 (32), 148 (12), 122 (8), 120 (8), 110 (14), 96 (70), 95 (69), 67 (68), 55 (12); HRMS (ESI) calculated for $[C_{14}H_{23}NO_3Br]^+$: 332.0861, found 332.0860.

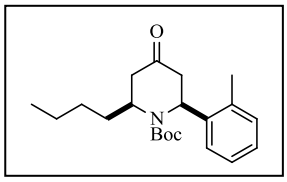
***(E)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone (51a).** Using general procedure A and ^{n}BuMgCl (0.63 mL, 1.6 M in THF, 1.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **23d** (143 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1-3% methanol:dichloromethane, v/v) gave colorless oil **51a** (154 mg, 89%). On the other hand, using General Procedure B and ^{n}BuLi (0.80 mL, 2.5 M in THF, 2.0 mmol), CuCN (89 mg, 1.0 mmol), LiCl (85 mg, 2.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **23d** (143 mg, 0.50 mmol) after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) gave colorless oil **51a** (152 mg, 88%). While the application of ^{n}BuMgCl (0.63 mL, 1.6 M in THF, 1.0 mmol), CuI (191 gm, 1.0 mmol), $BF_3.OEt_2$ (0.5 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **23d** (143 mg, 0.50 mmol) after purification by flash column chromatography (silica, 1-3%

methanol:dichloromethane, v/v) gave colorless oil **51a** (85 mg, 49% and **52a** (56 mg, 32.5%).



***(E)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone 51a:** IR (neat) 2960 (s), 2931 (s), 2861 (s), 1668 (s), 1367 (s), 1171 (s), 754 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 6.4 Hz, 3H), 1.28 (br s, 9H), 1.33-1.41 (m, 3H), 1.45-1.52 (m, 1H), 1.62 (br s, 1H), 1.90-1.99 (m, 1H), 2.31 (s, 3H), 2.65 (dd, J = 17.4, 33.9 Hz, 2H), 2.87 (dd, J = 6.0, 17.9 Hz, 1H), 3.07 (dd, J = 7.8, 17.4 Hz, 1H), 4.51 (br s, 1H), 5.55 (d, J = 6.9 Hz, 1H), 7.14 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.1, 22.5, 28.1, 28.9, 37.0, 42.4, 43.0, 51.3, 52.5, 80.1, 124.2, 126.1, 127.1, 131.1, 134.1, 141.3, 154.7, 206.9; mass spectrum *m/z* (relative intensity) EI, 345 (M^+, 0.1), 245 (13), 213 (10), 202 (30), 188 (88), 145 (100), 118 (13), 117 (76), 91 (51), 65 (15); HRMS (ESI) calculated for $[C_{21}H_{31}NO_3Na]^+$: 368.2202, found 368.2207.

***(Z)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone 52a**: IR (neat) 2972 (s), 29333 (s),



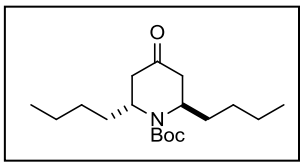
1664 (s), 1359 (s), 1172 (s), 1052 (s) 772 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 6.9 Hz, 3H), 1.17 (br s, 9H), 1.26-1.54 (m, 5H), 1.89 (br s, 1H), 2.34 (s, 3H), 2.58-2.75 (m, 4H), 4.61-4.67 (m, 1H), 5.31 (br s, 1H), 7.12-7.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.1, 22.4, 27.9, 29.1, 37.0, 43.5, 44.6, 51.7, 52.3, 80.4, 124.1, 126.6, 126.8, 130.5, 134.2, 142.9, 155.5, 208.1; mass spectrum *m/z* (relative intensity) EI 345 (M^+, 0.1), 274 (4), 245 (4), 213 (11), 210 (10), 188 (49), 146 (44), 145 (100), 117 (38), 115 (34), 91 (25), 65 (81); HRMS (ESI) calculated for $[C_{21}H_{31}NO_3Na]^+$: 368.2207, found 368.2202.

***(E)-N*-Boc-2-(2-methylphenyl)-6-(1-methylethyl)-4-piperidinone (51b).** Employing method B, general procedure A and using ^{i}PrMgBr (0.50 mL, 2.0 M in Et_2O, 1.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **23d** (143 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) gave pure **51b** (141 mg, 85 %): IR (neat) 2966 (m), 2925 (m), 2872 (w), 1723 (m), 1690 (s), 1460 (w), 1362 (s), 1339 (m), 1249 (m), 1170 (s), 1110 (m), 1019 (w), 974 (w), 861 (w), 767 (w), 748 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.15 (br s, 9H), 1.79-1.89 (m, 1H), 2.24 (s, 3H), 2.53 (d, J = 17.4 Hz, 1H), 2.62 (dd, J = 2.3, 17.8 Hz, 1H), 2.78 (dd, J = 5.9, 18.3 Hz, 1H), 2.99 (dd, J = 7.8, 17.4 Hz, 1H), 4.20 (br s, 1H), 5.45 (d, J = 7.3 Hz, 1H), 7.02-7.09 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.4, 20.5, 28.1, 35.0, 42.1, 43.2, 52.9, 56.6, 80.2, 124.0, 126.2, 127.1, 131.1, 134.1, 142.0, 155.5, 207.4; mass spectrum *m/z* (relative intensity) EI 331 (M^+, 0.09), 288 (26), 258 (2), 232 (30), 214 (1), 188 (81), 174 (4), 145 (93), 117 (17), 91 (12), 70 (6), 57 (100); HRMS (ESI) calculated for $[C_{20}H_{29}NO_3]^+$: 331.21528, found 331.21475.

***(E)-N*-Boc-2-(2-methylphenyl)-6-(1-phenylmethyl)-4-piperidinone (51c).** Employing method B, general procedure A and using benzylbromide (342 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **23d** (287 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) gave colorless crystals (337 mg, 89%). The stereochemistry of this molecule was determined by X-ray crystallography: m.p. 109.3-111.4 ^{o}C; IR (neat) 3449 (br, s), 2975 (s), 2854 (s), 1668 (s), 1366 (s), 1167 (s), 702 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (br s, 9H), 2.31 (s, 3H), 2.54 (d, J = 17.5 Hz, 1H), 2.66-2.78 (m, 3H), 3.00 (dd, J = 8.2, 18.0 Hz, 1H), 3.38 (dd, J = 3.2, 13.0 Hz, 1H), 4.77 (br s, 1H), 5.61 (br s, 1H), 7.15-7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 28.2,

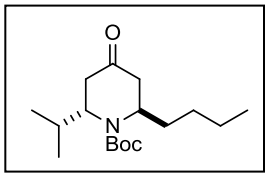
41.2, 43.0, 43.1, 52.8, 53.5, 80.5, 124.2, 126.1, 126.8, 127.2, 128.7, 129.5, 131.2, 137.7, 154.7, 206.5; mass spectrum *m/z* (relative intensity) EI 379 (M^+, 0.1), 279 (2.0), 207 (3.0), 188 (60), 145 (100), 117 (23), 91 (25), 70 (15), 65 (8).

***(E)*-*N*-Boc-2,6-di-*n*-butyl-4-piperidinone (53a).** Using general procedure A and ^{n}BuMgCl (0.63



mL, 1.6 M in THF, 1.0 mmol), *N*-Boc-2-*n*-butyl-2,3-dihydro-4-pyridone **23d** (127 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) gave colorless oil **53a** (138 mg, 89%): IR (neat) 2961 (m), 2927 (s), 1723 (m), 1693 (s), 1464 (w), 1359 (s), 1249 (s), 1113 (s), 977 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 6H), 1.22-1.35 (m, 10H), 1.48 (s, 9H), 1.78 (br s, 2H), 2.52 (d, J = 17.9 Hz, 2H), 2.68 (dd, J = 6.0, 17.9 Hz, 2H), 4.10 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.4, 28.4, 28.9, 36.7, 41.5, 51.0, 79.8, 154.6, 208.4; mass spectrum *m/z* (relative intensity) EI 311 (M^+, 0.74), 270 (3), 254 (75), 238 (18), 199 (40), 198 (99), 156 (34), 155 (28), 154 (100), 112 (93), 96 (13), 83 (15), 69 (33), 57 (99); HRMS (ESI) calculated for $[C_{18}H_{34}NO_3]^+$: 312.2539, found 312.2550.

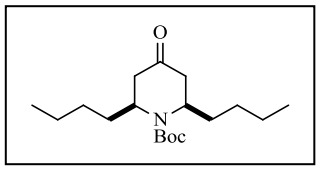
***(E)*-*N*-Boc-2-(1-methylethyl)-6-*n*-butyl-4-piperidinone (53b).** Using general procedure A and



^{i}PrMgBr (0.50 mL, 2.0 M in diethyl ether, 1.0 mmol), *N*-Boc-2-*n*-butyl-2,3-dihydro-4-pyridone **23d** (127 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) gave colorless oil **53b** (130 mg, 88%): IR (neat) 2961 (m), 2925 (m), 2867 (w), 1723 (m), 1691 (s), 1468 (w), 1367 (m), 1338 (m), 1252 (w), 1169 (m), 1101 (w), 1007 (w), 978 (w), 863 (w), 773 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.18-1.32 (m, 6H), 1.46 (s, 9H), 1.64-1.72 (m, 1H),

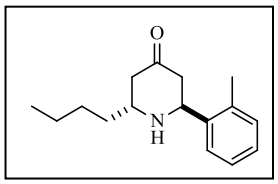
2.47 (dd, J = 2.7, 17.8 Hz, 1H), 2.56-2.60 (m, 2H), 2.62 (dd, J = 1.8, 6.4 Hz, 1H), 3.95 (br s, 1H), 4.00 (br s, 1H); ^{13}C NMR (125 Hz, $CDCl_3$)δ 14.1, 19.3, 20.3, 22.6, 28.5, 29.1, 34.8, 36.6, 41.8, 41.9, 51.8, 56.3, 80.0, 155.5, 209.0; mass spectrum *m/z* (relative intensity) EI 297 (M^+, 1), 296 (M^+-1, 6), 282 (1), 266 (3), 240 (53), 226 (13), 196 (39), 182 (14), 170 (2), 156 (6), 140 (29), 112 (28), 98 (6), 86 (7), 69 (20), 57 (100); HRMS (ESI) calculated for $[C_{17}H_{31}NO_3Na]^+$: 320.2202, found 320.2203.

***(Z)*-*N*-Boc-2,6-di-*n*-butyl-4-piperidinone (54a).** Employing general procedure B and ^{n}BuLi



(0.80 mL, 2.5 M in THF, 2.0 mmol), CuCN (89 mg, 1.0 mmol), LiCl (85 mg, 2.0 mmol), *N*-Boc-2-*n*-butyl-2,3-dihydro-4-pyridone **23d** (127 mg, 1.0 mmol) after purification by flash column chromatography (silica, 1-3% MeOH:CH_2Cl_2, v/v) gave colorless oil **54a** (135 mg, 86%): IR (neat) 2964 (m), 2923 (s), 1718 (m), 1689 (s), 1467 (w), 1361 (s), 1254 (s), 1110 (s), 976 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3H), 1.26-1.37 (m, 4H), 1.43-1.48 (m, 1H), 1.49 (s, 9H), 1.61-1.67 (m, 1H), 2.35 (d, J = 14.7 Hz, 1H), 2.68 (dd, J = 7.8, 14.7 Hz, 1H), 4.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 28.4, 29.1, 36.5, 43.7, 52.7, 80.1, 154.9, 209.0; mass spectrum *m/z* (relative intensity) EI 311 (M^+, 0.9), 270 (13), 254 (68), 238 (38), 199 (41), 198 (100), 156 (31), 155 (22), 154 (99), 112 (91), 96 (24), 83 (36), 69 (31), 57 (89); HRMS (ESI) calculated for $[C_{18}H_{33}NO_3Na]^+$: 334.2358, found 334.2355.

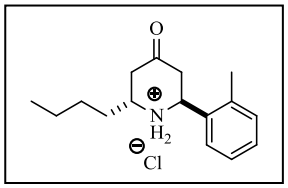
***(E)*-2-(2-Methylphenyl)-6-*n*-butyl-4-piperidinone (59).**[45] To the solution of *(E)*-*N*-boc-2-(2-



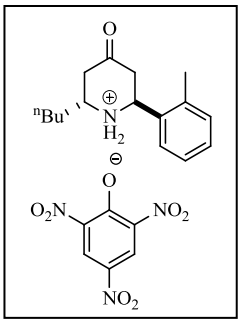
methylphenyl)-6-*n*-butyl-4-piperidinone (**51a**, 345 mg, 1.0 mmol) was added trifluoroacetic acid (228 mg, 2.0 mmol) in dichloromethane (5.0 mL) and the resulting mixture was stirred for 30 minutes at room temperature. The reaction was quenched with water (5.0 mL), neutralized using saturated sodium

bicarbonate solution, extracted with diethyl ether (3x10.0 mL), organic layer was washed with brine solution (10.0 mL), dried using anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo and purified by flash column chromatography (silica, 1-3% methanol:dichloromethane, v/v) to colorless oil **59** (233 mg, 95%). IR (neat) 3369 (br, s), 2957 (s), 2928 (s), 2859 (s), 1688 (s), 1598 (s), 1460 (s), 1379 (s), 1070 (s), 755 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.24-1.35 (m, 4H), 1.41-1.51 (m, 1H), 1.54-1.62 (m, 1H), 1.79 (br s, 1H), 2.30 (dd, J = 4.6, 13.8 Hz, 1H), 2.39 (s, 3H), 2.54-2.64 (m, 2H), 2.75 (dd, J = 5.5, 14.2 Hz, 1H), 3.29-3.35 (m, 1H), 4.57 (dd, J = 4.6, 8.3 Hz, 1H), 7.18-7.48 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.2, 22.4, 28.2, 33.3, 47.3, 48.1, 51.0, 52.8, 126.0, 126.3, 127.3, 130.7, 135.3, 140.6, 210.0; mass spectrum *m/z* (relative intensity) EI 245 (M^+, 6.0), 202 (20), 188 (55), 145 (100), 118 (34), 91 (21), 86 (23), 70 (13), 65 (15).

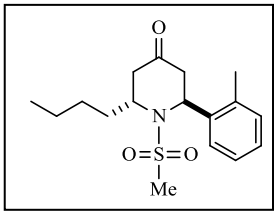
***(E)*-2-(2-Methylphenyl)-6-*n*-butyl-4-piperidinium chloride (60).** To the solution of 2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone (**59**, 61 mg, 0.25 mmol) in methanol (2.0 mL) was added 1.0 M HCl (0.5 mL) and the resulting mixture was stirred for 30 minutes at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10.0 mL) and anhydrous $MgSO_4$ was added. The filteration of mixture followed by evaporation of solvent gave **60** as a pale yelow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 6.9 Hz, 3H), 1.17-1.27 (m, 4H), 1.45-1.52 (m, 1H), 1.89 (br s, 1H), 2.36 (s, 3H), 2.45 (d, J = 15.1 Hz, 1H), 2.60 (d, J = 15.2 Hz, 1H), 3.11 (t, J = 13.3 Hz, 1H), 3.21 (d, J = 14.7 Hz, 1H), 3.38-3.44 (m, 1H), 4.70 (dd, J = 11.0, 3.3 Hz, 1H), 7.16-7.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 19.7, 22.2, 27.8, 29.8, 42.5, 44.5, 50.7, 53.9, 126.9, 127.3, 129.8, 131.5, 132.0, 136.6, 202.8.



***(E)*-2-(2-Methylphenyl)-6-*n*-butyl-4-piperidinium picrate (62).** The picrate salts of 2-(2-methylphenyl)-6-butyl-4-piperidinone (**59**) was prepared using the slight modification of literature procedure.[46] To the solution of **59** (62 mg, 0.25 mmol) in EtOH (4.0 mL) was added picric acid (57 mg, 0.25 mmol) and the resulting reaction mixture was stirred for 30 minutes at 60 ^{o}C before cooling to the room temperature. The filteration of mixture gave **62** as a red residue. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 6.4 Hz, 3H), 1.16-1.39 (m, 6H), 1.24 (br s, 1H), 1.89 (br s, 1H), 2.36 (s, 3H), 2.73 (dd, J = 38.5, 12.9 Hz, 2H), 3.22 (br s, 1H), 3.86 (br s, 1H), 5.03 (br s, 1H), 7.01-7.24 (m, 4H), 7.51 (br s, 1H) 8.75 (s, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 19.1, 22.1, 27.5, 30.9, 41.8, 43.8, 51.8, 54.2, 126.7, 126.9, 127.3, 128.9, 130.0, 131.5, 132.1, 135.9, 141.1, 161.4, 203.1.

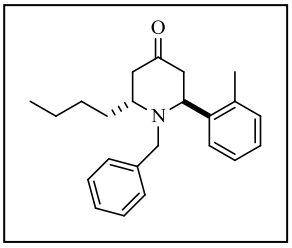


***(E)*-*N*-Methylsulfonyl-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone (64).** The protection of 2-(2-methylphenyl)-6- *n*-butyl-4-piperidinone (**59**) with methanesulfonyl chloride was carried out using slight modification of the procedure.[36] To the solution of **59** (74 mg, 0.3 mmol) in CH_2Cl_2 was added $MeSO_2Cl$ (68 mg, 0.6 mmol) and Et_3N (123 mg, 1.2 mmol) at 0 ^{o}C under argon and the reaction mixture was stirred for 2 hours at that temperature. The reaction was quenched with H_2O (5.0 mL), extracted with CH_2Cl_2 (3 x 5.0 mL), combined organic layer was washed with saturated aqueous NH_4Cl (5.0 mL), dried over anhydrous $MgSO_4$, filterred and solvent evaporated in rota vacuo. The purification of product by flash chromatography (1-2% MeOH:CH_2Cl_2, v/v) gave pure **64** (63 mg, 65%) as a viscous colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 1.22-1.32 (m, 4H), 1.59-1.67 (m, 1H), 1.74-1.82 (m, 1H), 2.33 (s, 3H), 2.35 (s, 3H), 2.56-2.71 (m, 3H), 3.33 (dd, J = 14.7, 9.2 Hz, 1H), 4.27-4.32 (m, 1H), 5.07



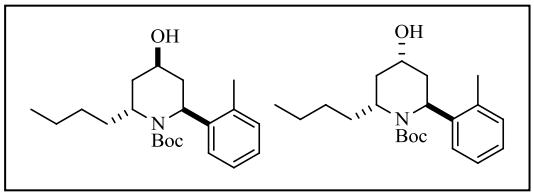
(dd, J = 9.2, 4.6 Hz, 1H), 7.13-7.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 19.4, 22.4, 29.2, 33.4, 43.4, 45.2, 45.5, 53.9, 55.1, 126.4, 128.9, 129.0, 130.8, 134.8, 137.2, 207.4.

***(E)*-*N*-Phenylmethyl-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone (64).** The benzyl protection of *(E)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone (**51a**) was carried out by slight modification of literature procedure.[35] To the solution of **51a** (62 mg, 0.25 mmol) was added K_2CO_3 (87 mg, 0.63 mmol) and $PhCH_2Br$ (52 mg, 0.3 mmol) in dry acetonitrile (3.0 mL) under argon at room temperature. The reaction mixture was refluxed for 16 hours and then cooled to room temperature. The removal of solid by filtration, solvent evaporation followed by purification of curde product using flash column chromatography (10-20% EtOAc:petrolium ether, v/v) gave **64** as a amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (t, J = 7.4 Hz, 3H), 1.00-1.28 (m, 5H), 1.62-1.71 (m, 1H), 2.21-2.29 (m, 1H), 2.34 (s, 3H), 2.39-2.44 (m, 1H), 2.65-2.75 (m, 2H), 3.01-3.07 (m, 1H), 3.38 (d, J = 13.8 Hz, 1H), 3.53 (d, J = 13.8 Hz, 1H), 4.38 (dd, J = 10.5, 3.2 Hz, 1H), 7.07-7.42 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 19.5, 22.5, 27.1, 29.0, 43.5, 45.9, 51.2, 56.2, 56.7, 126.3, 126.9, 127.0, 127.3, 128.2, 128.4, 130.8, 136.5, 139.6, 139.5, 210.0.



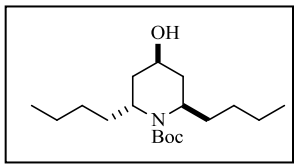
General Procedure D: Reduction of 2,6-Disubstituted 4-Piperidinones.[47] To the solution of 2,6-disubstituted 4-piperidinone (1.0 equivalent) was added $NaBH_4$ (2.0 equiv) in methanol and the resulting mixture was stirred for 30 mins at room temperature. The reaction mixture was quenched with saturated NH_4Cl (5.0 mL) and extracted with Et_2O (3x10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in rota vacuo and purified by flash column chromatography (silica, 20-25% ethyl acetate: petroleum ether, v/v).

***(E)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinol (65).** Employing general procedure D and using *(E)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone (70 mg, 0.2 mmol, **51a**) and



$NaBH_4$ (15 mg, 0.4 mmol) after purification by flash column chromatography (silica, 20-25% ethyl acetate: petroleum ether, v/v) gave colorless oil **65** along with other minor isomer (63 mg, 91%, 75:25 dr at CHOH): IR (neat) 3402 (br s), 2961 (s), 2926 (s), 2857 (s), 1655 (s), 1543 (s), 1366 (s), 1172 (s), 1066 (s), 792 (s); Major: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 6.0 Hz, 3H), 1.02 (s, 9H), 1.16-1.33 (m, 5H), 1.50-1.69 (m, 4H), 2.14-2.23 (m, 2H), 2.26 (s, 3H), 3.94-3.99 (m, 1H), 4.35 (br s, 1H), 4.64 (dd, J = 4.2, 9.2 Hz, 1H), 7.01-7.21 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.4, 22.6, 27.8, 28.1, 29.3, 32.3, 35.6, 40.8, 51.8, 53.6, 64.2, 79.6, 125.1, 126.1, 130.4, 133.8, 143.3, 156.1; mass spectrum *m/z* (relative intensity) EI 347 (M^+, 0.1), 220 (27) 205 (100), 189 (4), 177 (11), 145 (12), 105 (8), 57 (26); Minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, J = 7.3 Hz, 3H), 1.00 (s, 9H), 1.78-1.85 (m, 1H), 1.98-2.03 (m, 1H), 2.24 (s, 3H), 3.81 (s, 1H), 3.94-3.99 (m, 1H), 5.23 (s, 1H), 7.01-7.21 (m, 4H), rest of other hydrogen were imbedded underneath major isomer hydrogens; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.2, 22.5, 28.1, 29.1, 29.7, 35.4, 35.9, 36.5, 52.8, 63.4, 79.4, 125.2, 125.5, 126.5, 130.8, 135.1, 143.5, 155.4; HRMS (ESI) calculated for $[C_{21}H_{33}NO_3Na]^+$: 370.2358, found 370.2360.

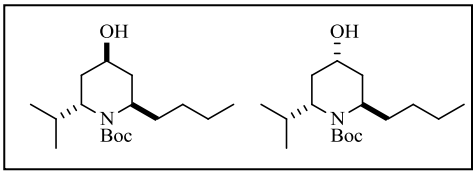
***(E)*-*N*-Boc-2,6-di-*n*-butyl-4-piperidinol (66).** Employing general procedure D and using *(E)*-*N*-



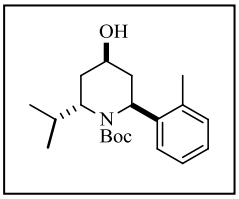
Boc-2,6-di-*n*-butyl-4-piperidinone (78 mg, 0.25 mmol, **53a**) and $NaBH_4$ (19 mg, 0.5 mmol) after purification by flash column chromatography (silica, 20-25% ethyl acetate: petroleum ether, v/v) gave colorless oil **66** (75 mg, 96%): IR (neat) 3447 (br, s), 2941 (s), 2909 (s), 2830 (s), 1681 (s), 1666 (s), 1423 (s), 1233 (s), 1069 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.4 Hz,

3H), 0.92 (t, J = 6.9 Hz, 3H), 1.25-1.36 (m, 9H), 1.46 (s, 9H), 1.60-1.71 (m, 4H), 1.89-1.95 (m, 1H), 1.99-2.06 (m, 3H), 3.41-3.51 (m, 1H), 4.09 (br s, 1H), 4.07-4.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2-carbons), 22.5, 22.6, 28.5, 29.0, 29.4, 32.6, 34.9, 35.3, 36.4, 51.5, 51.7, 64.7, 79.2, 155.4; mass spectrum *m/z* (relative intensity) EI 313 (M^+, 0.07), 256 (35), 240 (38), 213 (7), 200 (98), 156 (100), 138 (57), 112 (31), 95 (18), 69 (33), 57 (93); HRMS (ESI) calculated for $[C_{18}H_{36}NO_3]^+$: 314.2695, found 314.2686.

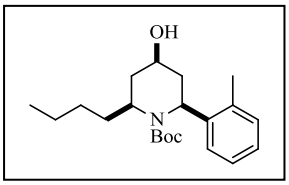
***(E)*-*N*-Boc-2-(1-methylethyl)-6-*n*-butyl-4-piperidinol (67).** Employing general procedure D and using *(E)*-*N*-Boc-2-(1-methylethyl)-6-*n*-butyl-4-piperidinone (70 mg, 0.2 mmol, **53b**) and $NaBH_4$ (15 mg, 0.4 mmol) after purification by flash column chromatography (silica, 20-25% ethyl acetate: petroleum ether, v/v) gave colorless oil **67** (52 mg, 87%, 1:1 dr at CHOH): IR (neat) 3412 (br s), 2975 (s), 2931 (s), 1664 (s), 1539 (s), 1359 (s), 1163 (s), 1075 (s), ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88-0.96 (m, 18H), 1.21-1.39 (m, 8H), 1.46 (s, 18H), 1.47-1.59 (m, 6H), 1.75-1.83 (m, 3H), 1.90-1.96 (m, 3H), 1.99-2.06 (m, 3H), 2.28-2.35 (m, 1H), 2.98-3.07 (m, 1H), 3.17-3.23 (m, 1H), 3.62-3.68 (m, 1H), 3.91-4.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4 (2-carbons), 19.8, 20.1, 20.5, 20.8, 22.5, 22.6, 22.7, 28.5 (2-carbons), 28.9 (2-carbons), 29.5, 30.9, 34.2, 35.1, 35.6, 36.6, 38.3, 52.2, 52.3, 58.5, 59.2, 66.0 (2-carbons), 79.3 (2-carbons), 156.3, 156.4; mass spectrum *m/z* (relative intensity), major: EI 299 (M^+, 0.01), 256 (21), 226 (6), 201 (22), 200 (100), 186 (11), 157 (11), 156 (90), 142 (12), 138 (29), 112 (32), 111 (12), 98 (11), 57 (99), 41 (36); HRMS (ESI) calculated for $[C_{17}H_{33}NO_3Na]^+$: 322.2358, found 322.2367.



***(E)*-*N*-Boc-2-(2-methylphenyl)-6-(1-methylethyl)-4-piperidinol (68).** Employing general procedure D and using *(E)*-*N*-Boc-2-(2-methylphenyl)-6-(1-methylethyl)-4-piperidinone (70 mg, 0.2 mmol, **51b**) and $NaBH_4$ (15 mg, 0.4 mmol) after purification by flash column chromatography (silica, 20-25% ethyl acetate: petroleum ether, v/v) gave colorless oil **68** along with other minor isomer (62 mg, 93%): IR (neat) 3431 (br s), 2955 (s), 2933 (s), 2872 (s), 1643 (s), 1371(s), 1273 (s), 1166 (s), 752 (s); Major: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (dd, J = 6.4, 8.3 Hz, 6H), 1.10 (s, 9H), 1.23 (br s, 1H), 1.74-2.07 (m, 3H), 2.29-2.35 (m, 1H), 2.35 (s, 3H), 2.39-2.42 (m, 1H), 4.02-4.11 (m, 1H), 4.14-4.18 (m, 1H), 4.81 (dd, J = 5.1, 11.9 Hz, 1H), 7.11-7.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 20.0, 20.9, 27.8, 31.4, 35.2, 39.2, 52.0, 58.2, 64.3, 79.3, 125.4, 126.0, 126.3, 130.6, 134.2, 142.9, 156.3. Minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (dd, J = 6.9, 21.5 Hz, 6H), 1.12 (s, 9H), 1.26 (s, 1H), 1.42-1.48 (m, 2H), 2.34 (s, 3H), 3.48-3.52 (m, 1H), 4.02-4.11 (m, 1H), 5.32 (br s, 1H), 7.11-7.30 (m, 4H); other hydrogens were imbedded underneath the major isomer hydrogens); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2 (2-carbons), 20.4, 28.1, 29.6, 33.0, 34.8, 53.6, 57.6, 63.6, 79.8, 125.2, 125.5, 126.5, 130.8, 134.1, 142.8, 155.7; mass spectrum *m/z* (relative intensity) EI 333 (M^+, 0.02), 207 (3), 190 (100), 172 (10), 147 (57), 129 (21), 117 (16), 105 (8), 91 (16); HRMS (ESI) calculated for $[C_{20}H_{31}NO_3Na]^+$: 356.2202, found 356.2202.

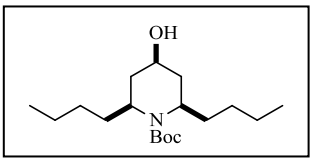


***(Z)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinol (69).** Employing general procedure D and using *(Z)*-*N*-Boc-2-(2-methylphenyl)-6-*n*-butyl-4-piperidinone (35 mg, 0.1 mmol, **52a**) and $NaBH_4$ (8 mg, 0.2 mmo1) after purification by flash column chromatography (silica, 20-25% ethyl acetate: petroleum ether, v/v) gave colorless oil **69** (29 mg, 84 %): IR (neat) 3448 (br s), 2961 (s), 2930 (s), 2859 (s), 1687 (s), 1366 (s), 1171 (s), 1071 (s), 782 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H), 1.26 (br s, 1H), 1.40-1.47 (m, 4H), 1.65-1.78 (m,

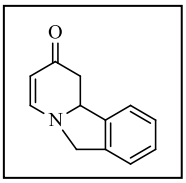


3H), 2.02-2.08 (m, 1H), 2.16-2.25 (m, 1H), 2.36 (s, 3H), 2.37-2.44 (m, 1H), 4.07-4.13 (m, 1H), 4.22-4.28 (m, 1H), 4.89 (dd, J = 5.1, 12.5 Hz, 1H), 7.12-7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 19.0, 22.7, 28.0, 29.3, 37.0, 38.3, 39.6, 51.7, 53.8, 65.6, 79.5, 124.4, 126.1, 126.3, 130.2, 133.6, 144.4, 155.8; mass spectrum *m/z* (relative intensity) EI 347 (M^+, 0.7), 220 (33) 205 (100), 189 (14), 177 (17), 145 (9), 105 (12), 57 (34); HRMS (ESI) calculated for $[C_{21}H_{34}NO_3]^+$: 348.2539, found 348.2531.

***(Z)-N*-Boc-2,6-di-*n*-butyl-4-piperidinol (70).** Employing general procedure D and using (*Z*)-*N*-Boc-2,6-di-*n*-butyl-4-piperidinone (78 mg, 0.25 mmol, **54a**) and $NaBH_4$ (19 mg, 0.5 mmol) after purification by flash column chromatography (silica, 20-25% ethyl acetate: petroleum ether, v/v) gave colorless oil **70** (68 mg, 87%): IR (neat) 3433 (br, s), 2931 (s), 2869 (s), 1687 (s), 1662 (s), 1409 (s), 1365 (s), 1175 (s), 1095 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 6H), 1.26-1.34 (m, 8H), 1.46 (s, 9H), 1.49-1.60 (m, 4H), 1.71-1.79 (m, 3H), 2.14 (m, 2H), 3.89-3.93 (m, 1H), 4.11-4.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 28.5, 29.0, 36.1, 38.1, 50.3, 65.8, 79.2, 155.4; mass spectrum *m/z* (relative intensity) EI 313 (M^+, 0.08), 256 (25), 240 (5), 200 (100), 156 (99), 138 (26), 112 (54), 95 (8), 69 (25), 57 (98); HRMS (ESI) calculated for $[C_{18}H_{36}NO_3]^+$: 314.2695, found 314.2703.

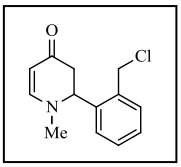


1,10b-Dihydropyrido[2,1,α]isoindole-2-one (71). The cyclization of compound **24r** to tricyclic compound **71** was carried out using literature procedure.[18] To the solution of *N*-Boc-2-(2'chloromethylphenyl)-2,3-dihydro-4-pyridone **24r** (161 mg, 0. 5 mmol) in methanol (5.0 mL) was added sodium metal (48 mg, 2.0 mmol) and the mixture was heated to reflux for 1 hour. The mixture was concentrated in vacuo and purified by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave white pure solid **71** (71



mg, 77 %) as a major product: m.p. 134.7-136.1 ^{o}C; IR (neat) 2961 (m), 2944 (s), 1715 (m), 1464 (w), 1363 (s), 1241 (s), 1170 (s), 1010 (m), 934 (w), 737 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (t, J = 16.5 Hz, 1H), 2.81 (dd, J = 5.0, 17.0 Hz, 1H), 4. 85 (dd, J = 14.0, 34.5 Hz, 2H), 5.11 (d, J = 7.0 Hz, 1H), 5.22 (dd, J = 4.5, 16.0 Hz, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.8, 54.5, 62.7, 98.7, 122.1, 122.9, 128.3 (2-carbons), 136.6, 139.6, 149.6, 191.3; mass spectrum *m/z* (relative intensity) EI 186 (M^++1, 14.34), 185 (M^+, 100), 168 (17), 157 (15), 156 (52), 142 (8), 130 (17), 129 (20), 115 (34), 91 (9), 77 (11), 65 (6), 51 (8); HRMS (ESI) calculated for $[C_{12}H_{11}NO]^+$: 185.08407, found 185.08450.

***N*-Methyl-2-(2-chloromethylphenyl)-2,3-dihydro-4-pyridone (72).** Attempted cyclization of *N*-Boc-2-(2'chloromethylphenyl)-2,3-dihydro-4-pyridone **24r** (161 mg, 0.5 mmol) using sodium metal (48 mg, 2.0 mmol) in methanol after purification by flash column chromatography (silica, 1-3 % MeOH:CH_2Cl_2, v/v) gave **72** as a minor product (8 mg, 7%): IR (neat) 2977 (w), 1756 (s), 1671 (s), 1613 (s), 1383 (s), 1310 (b), 1213 (s), 1155 (s), 739 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (dd, J = 16.1 Hz, 5.1 Hz, 1H), 2.79-2.85 (m, 1H), 4.39 (d, J = 11.0 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 5.13 (d, J = 7.4 Hz, 1H), 5.51 (br s, 1H), 7.22-7.56 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.9, 54.0, 58.3, 73.2, 99.4, 126.8, 128.3, 129.3, 130.9, 192.4.



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CHAPTER V

REGIOSELECTIVE 1,4-CONJUGATE ADDITION OF GRIGNARD REAGENTS TO NITRODIENES AND THIODIEONATES CATALYZED BY ZINC(II) SALTS

5.1. 1,4-CONJUGATE ADDITION TO NITRODIENES

5.1.1 Introduction

The conjugate addition reaction of organometallic reagents to Michael substrates is one of the most studied methods for the construction of carbon-carbon bonds in organic chemistry.[1] An area of synthetic methodology focused on selective conjugate addition reactions under mild reaction conditions has attracted significant interest from organic chemist in recent years. Common Michael acceptors such as α,β-unsaturated carbonyls, nitriles, phosphates, sulfones, nitro compounds and their extended analogues have proven versatile substrates for conjugate addition reactions.[2,3] The presence of conjugation propagates the electronic effect of the functional group through the π-system and hence nucleophilic addition to α,β-unsaturated system usually occurs at the β-position. However, propagation of the electronic effect via two double bonds principally create additional sites for the nucleophilic attack leading to 1,6-addition products especially with organocuprate reagents. The presence of extended π-conjugation also creates difficulty in controlling the regioselectivity thus leading to mixture of 1,2-, 1,4- or 1,6-adducts which justifies the least exploration of such methodologies. Although, it's hard to substantiate a single factor for effecting the regioselective 1,4- or 1,6-conjugate addition to extended Michael substrate, several factors including the nature of nucleophiles and the stereoelectronic effect of substrates are expected to govern the reactive sites for the conjugate addition reactions.[4]

Organometallic reagents such as organolithium, organomagnesium and the corresponding cuprate or zincate reagents are the most common nucleophiles used for the conjugate addition reactions. Other organometallic reagents such as R_2Zn, R_3ZnLi, R_3Al, RBX_2 are also employed for conjugate addition reactions.[2] A large number of organocatalysts[5] or transition metals such as copper,[6-9] iron,[10, 11] nickel,[12] ruthenium,[13, 14] and iridium,[15, 16] catalyze regio- and stereoselective 1,6-conjugate addition reactions[14, 17] of organometallic reagents to extended Michael substrate are reported in the literature. Despite the appealing success in these systems, regioselective 1,4-conjugate addition reaction to extended Michael substrates has been poorly explored. Previous reports of uncatalyzed 1,4-addition of Grignard reagents[10, 18] or organolithium reagents[19, 20] to electron deficient dienes offered partial success with moderate yields of corresponding products.

Nitroalkenes are highly attractive Michael substrates that undergo conjugate addition reactions with organometallic reagents. The nitro group acts as a masked functionality and can be readily converted into a varietiey of functional groups. The nitro group can be converted into carbonyl groups in the classical Nef reaction,[21] while dehydration of primary nitro groups give nitrile oxides and oxidation of the nitro group give carboxylic acids. Reduction of the nitro group gives corresponding ketones, oximes, hydroxylamines or amines.[22,23] The strong electron withdrawing nature of the nitro group controls the reactivity while promoting the reactions of these substrate in the presence of other functional groups. β-Nitrostyrene, $\alpha,\beta,\gamma,\delta$-unsaturated nitrodienes and a nitroenyne are common nitro-Michael subsrate used for conjugate addition reactions. A brief overview on regio- and stereoselective conjugate addition reactions of various nucleophiles to nitro-Michael substrate will be summerized in this chapter.

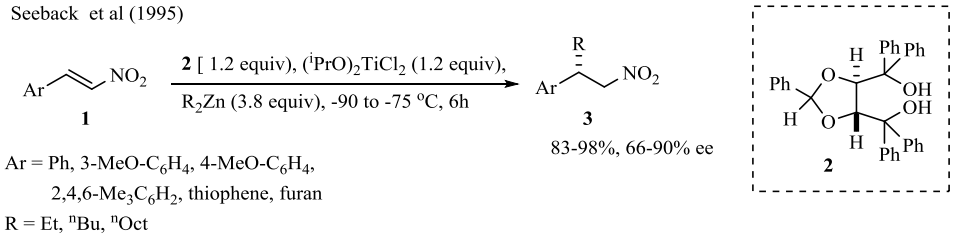
5.1.2 Pioneering Study

5.1.21 Conjugate Addition to Nitroalkenes

Nitroalkenes are highly reactive Michael acceptors that undergo 1,4-conjugate addition reactions with a large number of organometallic reagents and anionic species. A large number of chemical transformations for enantioselective conjugate addition reaction of organometallic reagents to nitroalkenes are reported in the literature. Organozinc compounds are the reagents of choice for the conjugate addition reaction to *β*-nitrostyrene despite their major limitation involving low yields due to background radical,[24] polymerizations,[25] or the subsequent reactions with the nitronates[26] formed in the reaction.

The conjugate addition reaction of nucleophilic species to nitroalkene is effected by several Lewis acids. Seeback and Schafer reported an enantioselective 1,4-addition reaction of dialkylzinc to nitroalkene **1** using Lewis acid (e.g., $MgBr_2$, MgI_2 or chlorotitanates) as additives (**Scheme 5.1.1**). The reaction of dialkylzinc to nitroalkene **1** in the presence of titanium TADDOLate gave 1,4-adduct **3** in high yield and high enantioselectivity (83-98%, 68-90% ee).[27]

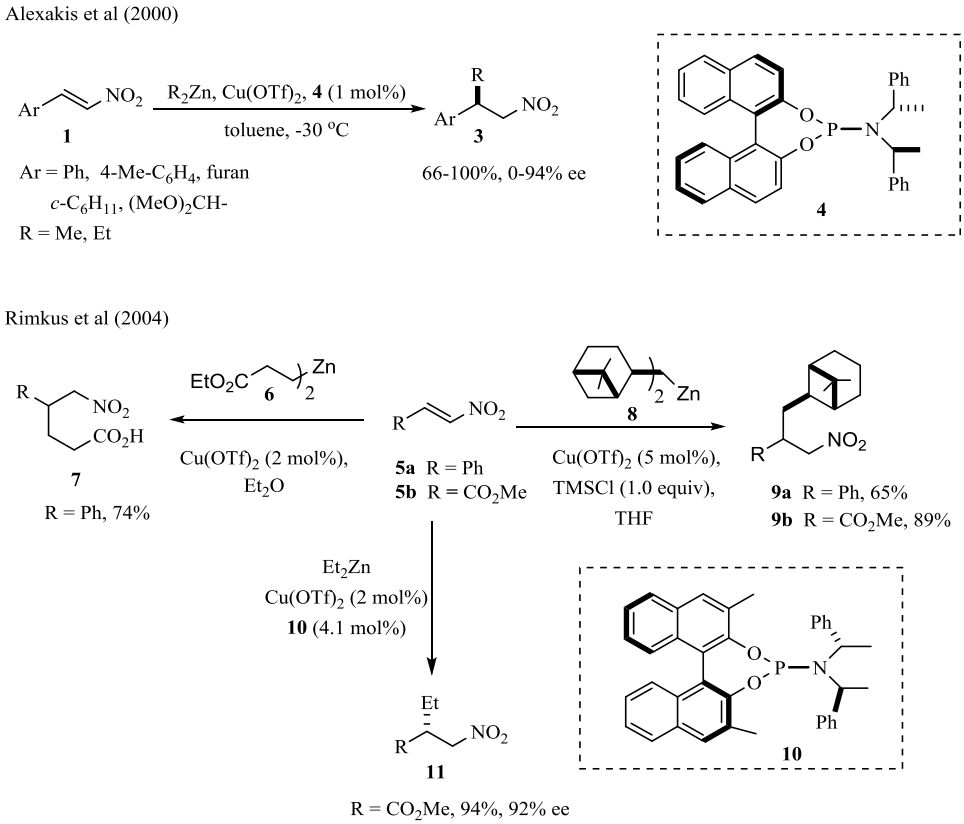
Scheme 5.1.1 Enantioselective 1,4-Conjugate Addition of Dialkylzinc to Nitroalkenes.[27]



Copper is an excellent catalyst for the 1,4-addition reaction of organometallic reagents to Michael substrates. We and other previously reported several examples for the 1,4-conjugate addition reaction of organocuprates and organozincates to Michael substrates (for details; see

chapter 1). $Cu(OTf)_2$ was proven as efficient catalyst for effecting the 1,4-addition for the nitrodiene. Alexakis and Benhaim[28] employed phosphoramidite catalysts for the enantioselective conjugate addition of Zn-Cu coupled reagents to nitroalkenes (**Scheme 5.1.2**). Screening of

Scheme 5.1.2 1,4-Addition of Functionalized Diorganozinc to Nitroalkenes.[28,29]



several catalysts showed that the catalytic amounts of chiral phosphoramide **4** and $Cu(OTf)_2$ are efficient for effecting 1,4-addition reaction affording corresponding products in high yields and none to good enantioselectivity (66-100%, 0-94% ee). In addition, Cu(II) salts also catalyzed the conjugate addition reaction of functionalized and non-functionalized diorganozinc to nitroalkenes.[29] The reaction of *bis*-[2-(ethoxycarbonyl)ethyl)zinc with *β*-nitrostyrene (i.e., **5a**) gave conjugate addition product **7** in good yields (74%). The reaction of enantiomerically pure dimyrtanylzinc **8** with **5a** and **5b** gave **9a** and **9b** in good yields but with no enantioselectivity (65

and 89% respectively). On the other hand, reaction of R_2Zn in the presence of catalytic amounts of chiral phosphoramidite **10** and copper (II) salts under identical reaction conditions gave **11** in good yield and good enantioselectivity (94%, 92% ee).

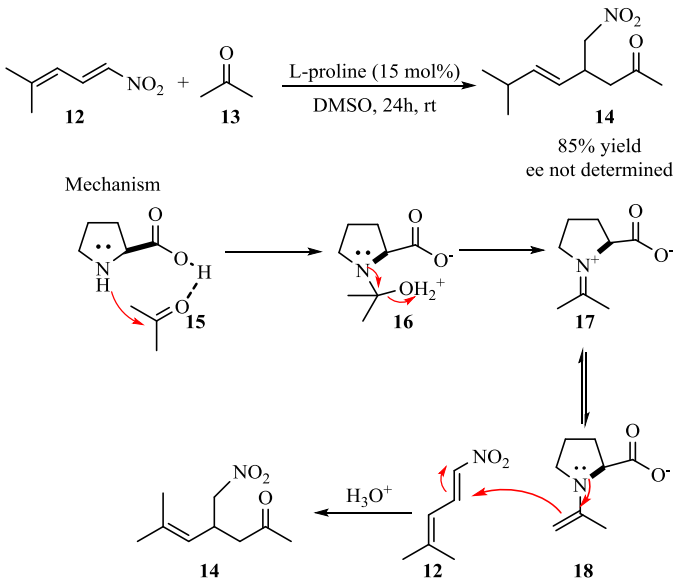
5.1.22 Conjugate Addition to Nitrodienes

The reaction of nucleophilic species to electron deficient conjugated dienes particularly in a regio- and stereocontrolled fashion is a daunting challenge for synthetic organic chemists.[17] Electron deficient dienes have more than one reactive site and reaction of nucleophiles with such substrates lead to a mixture of products. Nitrodienes despite their high reactivity, the chemistry of these substrates are significantly less explored possibly due to the difficulty in their preparation or lack of suitable synthetic techniques for transforming these compounds into useful biological targets.[30] In spite of the challenges associated with the substrates, nitrodienes are recently been used as reactive synthons for the synthesis of a few biologically important complex organic molecules.[31, 32]

A rapid upsurge in methodologies for enantioselective 1,4-conjugate addition reaction of aldehydes and ketones to nitrodienes employing organocatalytic systems occured in the last five years. Chiral proline,[33-36] bifunctional amine-thiourea derivatives,[37-41] cinchona alkaloids[42, 43] and aminoacids[44, 45] have dominated the literature reports for the regio- and enantioselective conjugate addition reactions of carbonyl substrates to nitrodienes with high efficiency. A brief overview on regio- and enantioselective conjugate addition reactions of carbonyl substrate to nitrodienes promoted by organocatalysts is summarized in the following section of the dissertation.

In 2001, List and coworkers[33] reported the first example on conjugate addition reaction of acetone to 1,3-nitrodiene **12** affording **14** in good yields (85%) catalyzed by L-proline and the reaction was assumed to proceed via enamine intermediates. It was proposed that the reaction of L-proline with acetone formed an imine **17**, which is in equilibrium with corresponding enamine **18.** The enamine intermediate **18** next undergo 1,4-conjugate addition to nitrodiene **12** affording the final product **14**. However, the authors did not measure the enantioselectivity of the product in this reaction.

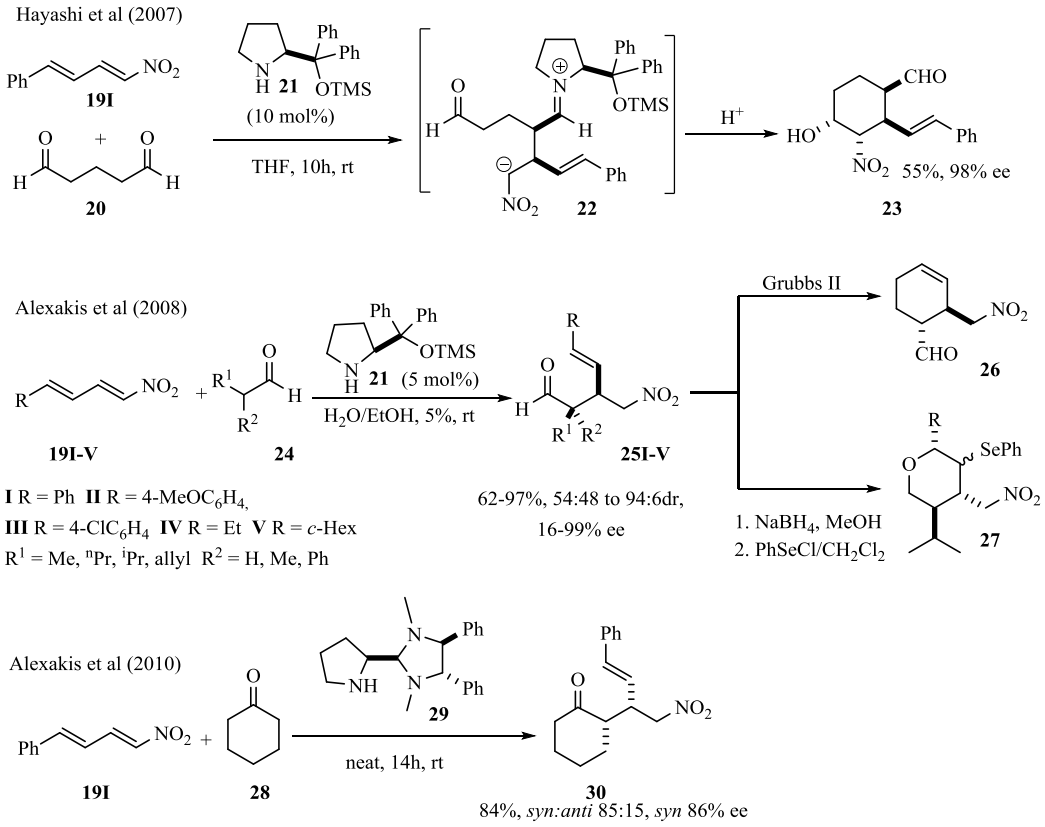
Scheme 5.1.3 L-Proline Catalyzed 1,4-Conjugate Addition of Acetone to Nitrodiene and Proposed Mechanism.[33]



In 2007, Hayashi and coworkers[34] reported a highly efficient diphenylprolinol silyl ether (i.e., **21**) catalyzed tandem Michael addition/ Henry reaction of pentane-1,5-dial (**20**) to 1-nitro-4-phenyl-1,3-butandiene (**19I**) for the synthesis of nitrocyclohexanecarbaldehyde **23** in moderate yields and excellent enantioselectivity (55%, 98% ee). The authors claimed that the reaction was

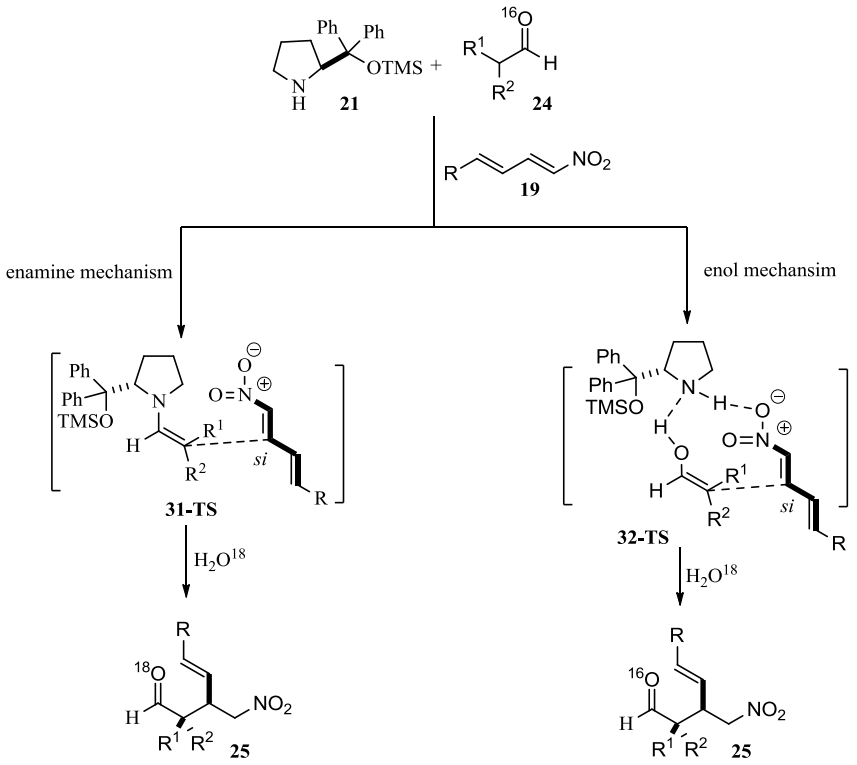
preceded via enamine intermediate with the involvement of zwitter ion **22**. Alexakis and coworkers[35] also employed prolinol catalyst **21** for the diastereo- and enantioselective 1,4-conjugate addition reactions of aldehyde **24** to nitrodiene **19I-V** in mixed solvent systems (5% water in ethanol) affording 1,4-adduct **25I-V** in high yields and with excellent enantioselectivity (62-97%, *syn/anti*; up to 94:6, s*yn* up to 99% ee). The substrate screening experiments confirmed that the presence of an electron rich substituent at the *para*- position of the aryl ring [e.g., MeO- in **19II**) or the use of an alkyl group (e.g., Et, *c*-hex, **19IV-V**) at the δ-position of nitrodiene diminished the diastereo- and enantioselectivity of the 1,4-adduct **25**. The synthetic versatility of the methodology was proven by the successful cyclization of **25** into chiral nitro-cyclohexene derivatives **26** using Grubbs II generation catalyst or selenocyclization to tetrahydropyran derivatives **27**. Chiral prolinol **29** also catalyzed the 1,4-conjugate addition reaction of cyclohexanone (**28**) to **19I** affording 1,4 adduct **30** in good yield and good enantioselectivity (84%, *syn:anti* 85:15, *syn* 86% ee).[36] In all of these papers, the authors nicely articulated the importance of proline based organocatalysts for the enantioselective 1,4-conjugate addition reactions of carbonyl substrates to nitrodienes for the synthesis of substituted nitrocyclohexene and nitrotetrahydropyran derivatives present in several natural products.

Scheme 5.1.4 Organocatalytic Enantioselective 1,4-Conjugate Addition Reactions to Nitrodienes.



A mechanistic study of the prolinol catalyzed enantioselective 1,4-conjugate addition of aldehydes and ketones to nitrodienes suggested the involvement of either enamine[46] or enol[47] intermediates in the reaction as both pathways offer the same stereochemical outcomes. In the enamine mechanism, the reaction of chiral (*S*)-diphenylprolinol silyl ether **21** with aldehyde **24** give an enamine intermediate, which interacts with 1,3-nitrodiene **19** to form **31-TS**. The *re* face of the nitrodiene in the **31-TS** is blocked by the bulky diphenylmethyl trimethylsilyl ether group. Hence the preferential *si* attack of an enamine to the *si* face of the nitrodiene gives the *syn*-conjugate addition product **25**. A mechanistic rationale for the involvement of enamine intermediate was confirmed by a controlled experiment using isotopically labeled water (H_2O^{18}) for the hydrolysis of **31-TS**, which showed the incorporation of labeled oxygen in the product **25**.

Scheme 5.1.5 Proposed Mechanism for the Enantioselective 1,4-Addition to Nitrodienes.[46,47]

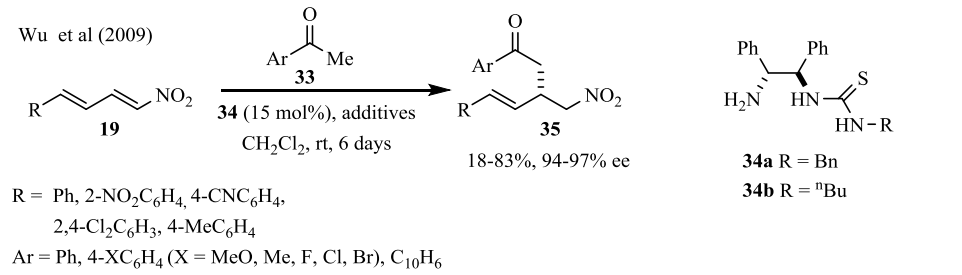


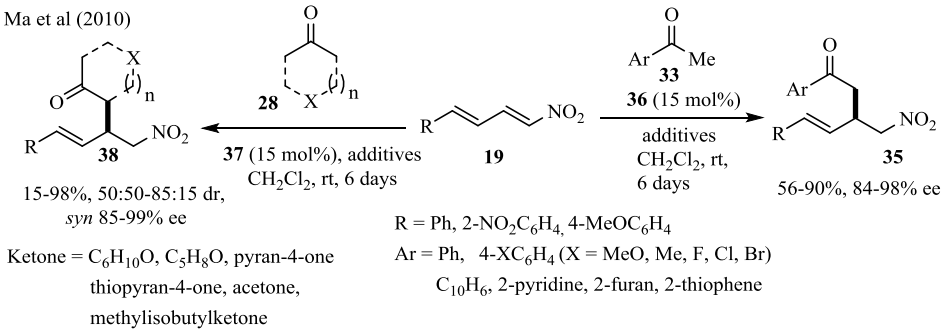
However in enol mechanism, the formation of association complex **32-TS** in the reaction of nitrodiene **19**, (*S*)-diphenylprolinol silyl ether **21** and aldehyde **24** was proposed. In **32-TS**, the *N*-atom of the catalyst gets hydrogen bonded with the enol hydrogen, while *N*-hydrogen in the catalyst also form hydrogen-bond with the nitro group. During this orientation, *si*-*si* interaction of enol with the nitrodiene is sterically less hindered and such attack of the reactants give the *syn*-adduct. Control experiment involving the hydrolysis of **32-TS** with isotopically label water gave the final product with no-incorporation of labeled oxygen confirming the participation of this mechanism.

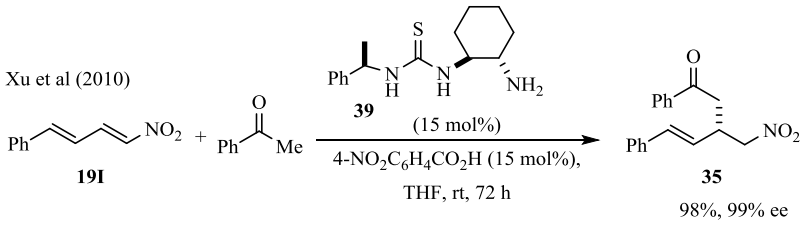
Although, organic chemist have long sought to apply the principle of bifunctional catalysis for asymmetric synthesis, the methodology was successfully employed with the

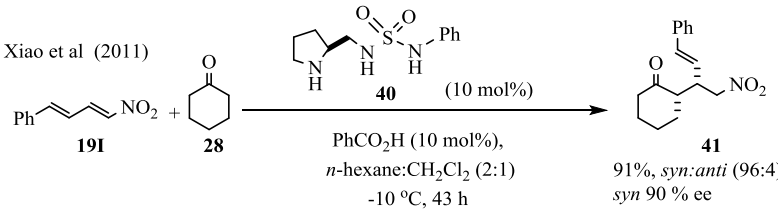
enantioselective 1,4-conjugate addition to nitrodienes only in the last few years. In 2009, Wu and coworkers[37] reported chiral thiourea based **34** catalyzed enantioselective 1,4-addition reaction of aromatic ketone **33** to nitrodiene **19I** (**Scheme 5.1.6**). Screening of several organocatalysts and solvents showed organocatalysts **34a** and **34b** in toluene offered the highest yields and enantioselectivity (up to 83% yield, up to 97% ee). Although attempted reaction of ketone using Brønsted acid (e.g., $PhCO_2H$ or AcOH) as an additive did not improve the yield and enantioselectivity, excess amounts of ketone and optimized substrate concentration (0.2 M) were proven essential for achieving the highest yields and enantioselectivity. In addition, application of electron deficient aromatic methyl ketones afforded better yield while the presence of electron-withdrawing or electron-donating group on the aromatic ring of the nitrodienes usually diminished the yields despites obtaining quite similar enantioselectivity. The precise mechanism for the bifunctional catalysis has not been fully understood partly due to their inherent complexity. However, the proposed mechanism for the reaction involved an activation of the nitrodienes via hydrogen bonding with the secondary amine unit of the organocatalyst while the primary amine unit of the catalyst forms an imine with acetophenone. One year later, Ma and coworkers[48] reported a similar protocol for the 1,4-conjugate addition of several ketones to nitrodiene catalyze by saccharide based bifunctional catalyst **36**. Unlike, Wu and coworker's previous report, yield and enantioselectivity were enhanced by the addition of additives (e.g., $PhCO_2H$:H_2O, 1:20-1:40). Screening of several saccharide based bifunctional catalysts during their study showed that chiral catalyst **36** was most effective for affording 1,4-adduct **35** in good yields and good to excellent enantioselectivity (56-90%, 84-98% ee). Although organocatalyst **36** failed to promote conjugate addition of cyclohexanone to nitrodiene, the application of nonrigid bifunctional catalyst **37** gave *syn*-Michael addition product in excellent yield and excellent enantioselectivity (15-94%, 85-95% ee).

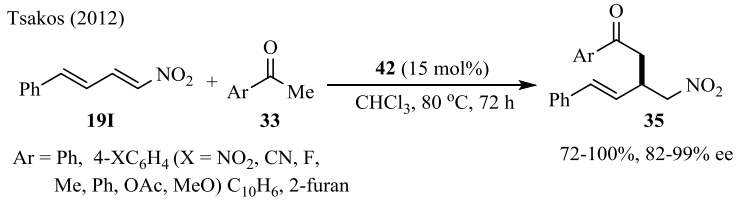
Scheme 5.1.6 Bifunctional Amine-thiourea Catalyzed Enantioselective 1,4-Addition Reaction to Nitrodienes.[37,39,40,48,49]

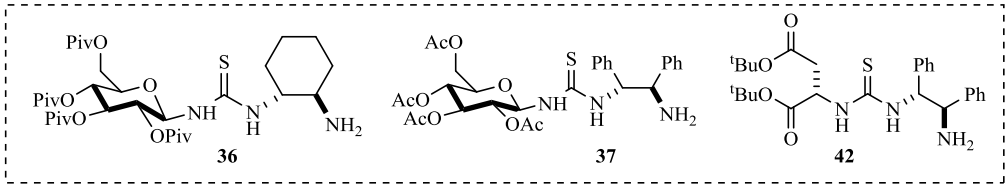






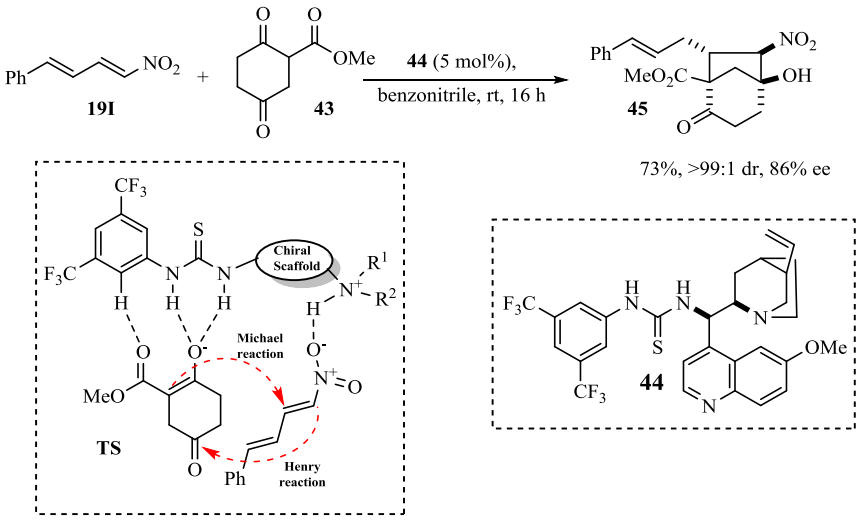






Xu and coworkers[49] used a similar amine-thiourea catalyst **39** for enantioselective 1,4-conjugate addition reaction of acetophenone to nitrodiene **19I** using 4-nitrobenzoic acid as an additive affording 1,4-adduct **35** in excellent yield and excellent enantioselectivity (98%, 99% ee). Pyrrolidinyl-sulfamide **40**[39] also catalyzed the enantioselective 1,4-conjugate addition reaction of cyclohexanone, while thiourea-amine based di-*tert*-butyl aspartate **42**[40] catalyzed the enantioselective 1,4-addition of aryl ketones to nitrodiene **19I** affording corresponding product **35** in excellent yield and excellent enantioselectivity (**41**, 91%, *syn:anti*, 96:4, *syn* 90% ee; **35**, 72-100%, 82-99% ee). In all of these reactions, thiourea based compounds acted as bifunctional catalysts and accetrated the reaction by binding both reactant molecules into a single transition state to effect the conjugate addition reaction.

Scheme 5.1.7 Enantioselective Henry-Michael Addition Reaction of Nitrodiene **19I**.[41]



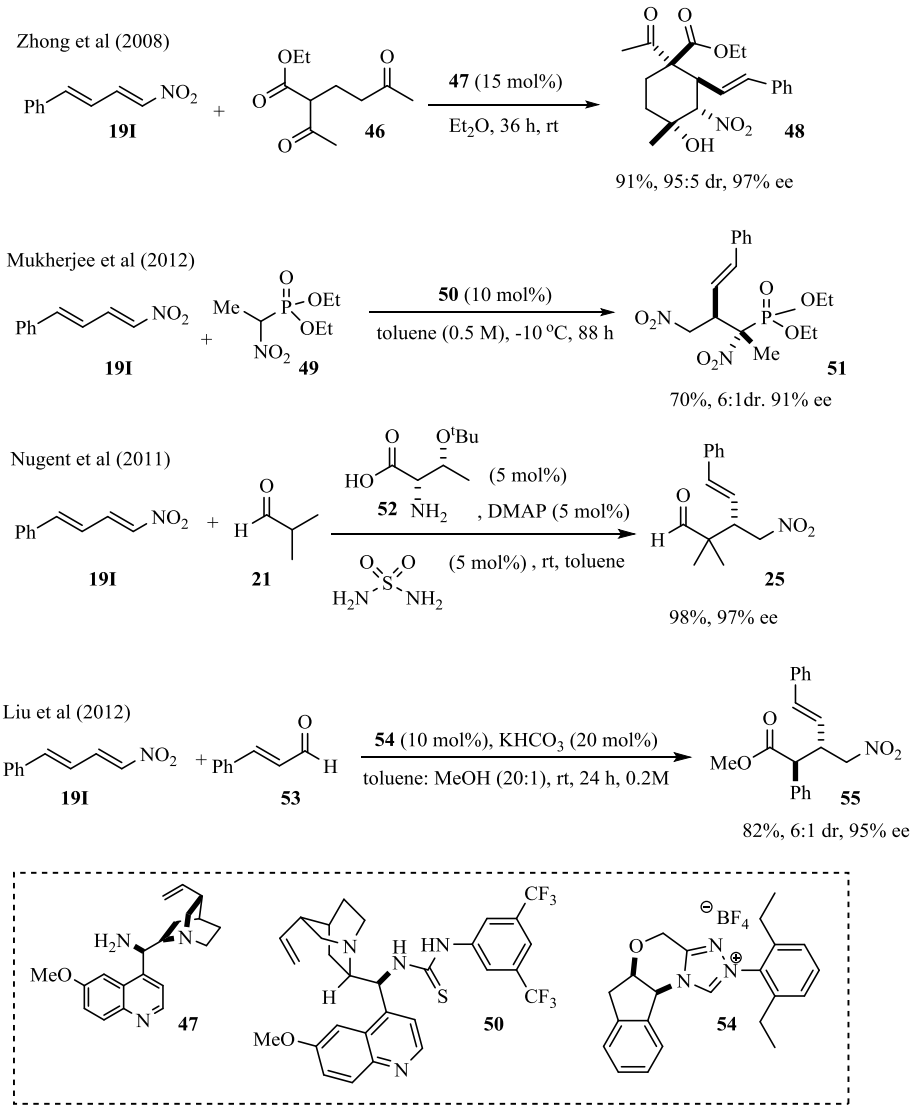
Chiral thiourea based chincona alkaloid **44** is an effective catalyst for the enantioselective Michael-Henry reaction of cyclic *β*-ketoester **43** with nitrodiene **19I** affording bicyclic-[3.2.1]-octane derivatives **45** in good yield and good enantioselectivity (**Scheme 5.1.7**, 73%, >99:1 dr,

86% ee).[41] This protocol allowed the facile synthesis of bicyclic compounds bearing four stereogenic centers in a one pot reaction.

A theoretical study using Density Functional Theory (DFT) calculation for the chincona alkaloid **44** catalyzed Henry-Michael addition reaction of cyclic *β*-ketoester **43** to nitrodiene **19I** suggested the involvement of an enol mechanism in the reaction. The enolization of *β*-ketoester **43** followed by hydrogen bonding of enol hydrogen with thiourea, simultaneous H-bonding of phenyl hydrogen with ester carbonyl and nitrodiene coordination with the tertiary amine unit of the catalysts was proposed in the **TS**. This multi-hydrogen bonding **TS** activated both the substrate and brings the enolic ester moiety of **43** and the thiourea unit of organocatalyst **44** together in the same plane. Hydrogen bonding of the catalyst with an enol and nitrodiene also minimized steric hindrance and thereby increased the stability of the transition state. The highly preferred enantioselectivity for (*R*,*S*)-enantiomer in the reaction was rationalize due to the more stabilized transition state energy for (*R*,*S*)-enantiomer of the product (-5.71 Kcal/mol) compared to that of (*S*,*R*) enantiomer. The participation of an enol mechanism was in accord with Wong's[47] earlier DFT calculations for the enantioselective oxyamination reaction of aldehydes with nitrosobenzene catalyzed by prolinol based organocatalyts. On the other hand, Tsogoeva and coworker's[46] DFT calculation for the nitro-Michael reaction of ketones catalyzed by thiourea based catalysts suggested the involvement of an enamine mechanism. Their study showed that hydrogen bonding between the amine hydrogen in the thiouera unit with one of the oxygen atoms in the nitro-group gave the lower energy transition state where the attack of the enamine to the nitro-Michael acceptor preferred attack from the *si*-face affording the final product in high enantiomeric excess.

Zhong and coworkers[41] reported that chiral chincona alkaloid **47** catalyzed enantioselective Michael-Henry reaction of 2-acetyl-5-oxohexanoate **46** with nitrodiene **19I** and the product of the reaction undergo subsequent cyclization to give **48** in excellent yield and excellent enantioselectivity (**Scheme 5.1.8**, 91%, 95:5 dr, 97% ee). Mukherjee and coworkers[43] reported

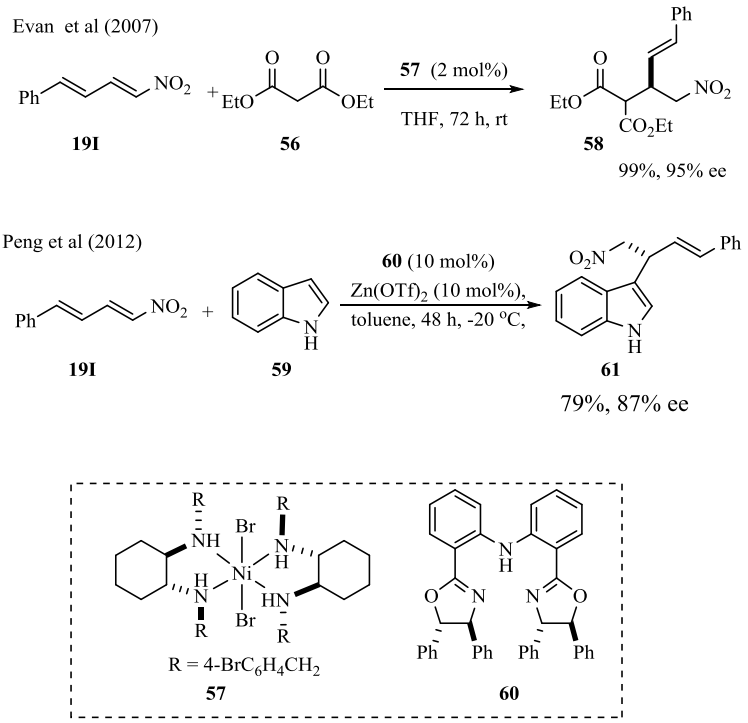
Scheme 5.1.8 Enantioselective 1,4-Conjugate Addition to Nitrodiene **19I**.[41,43-45]



quinine-based thiourea-tertiary amine **50** catalyzed enantioselective 1,4-conjugate addition reaction of α-substituted nitrophosphate **49** to nitrodiene **19I** affording product **51** with contiguous tertiary and quaternary stereogenic centers in moderate yield, diastereo- and enantioselectivity (70%, 6:1dr, 91% ee). The newly develop method can be used for the synthesis of α,β-disubstituted α,γ-diamino phosphoric acids present in several natural products. Besides, three component organocatalytic systems (i.e.; ^{t}BuO-L-threonine, sulfamide and DMAP) were also used for the enantioselective conjugate addition reaction of α-branched aldehyde **21** to nitrodiene **19I** affording 1,4-adduct **25** in excellent yield and excellent enantioselectivity (98%, 97% ee).[44] Recently, Liu and coworkers[45] reported an enantioselective 1,4-conjugate addition reaction of homoenolates (formed during the reaction of aldehyde **53** with in situ generated carbene) to nitrodiene **19I**. This reaction gave δ-nitro esters **55** in good yields, with moderate dr and good enantioselectivity (82%, 6:1 dr, 95% ee).

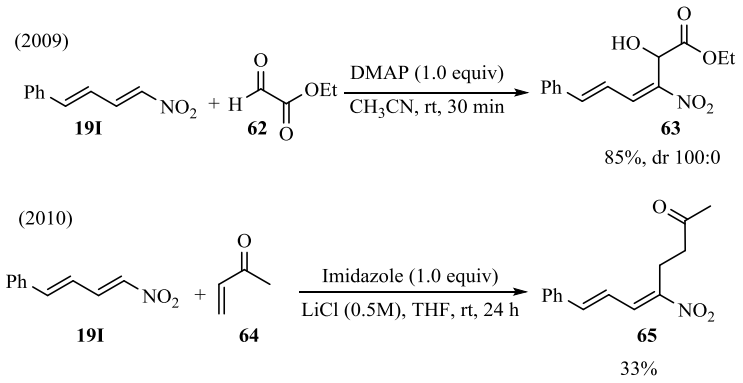
In addition to the above mentioned organocatalytic protocals, transition metal complexes are also effective for enantioselective 1,4-conjugate addition of malonates to nitrodienes (**Scheme 5.1.9**). Ni(II)-diamine complex **57** catalyzed enantioselective 1,4-conjugate addition of diethyl malonate **56** to nitrodiene **19I** gave **58** in excellent yield and good enantioselectivity (99%, 95% ee),[50] while corresponding bis-(oxazoline)**60**–$Zn(OTf)_2$ complex catalyzed Friedal Craft alkylation of indole **59** with nitrodiene **19I** affording 1,4-adduct **61** in moderate yield and moderate enantioselectivity (79%, 84% ee).[51]

Scheme 5.1.9 Transition Metal Complexes Catalyzed Enantioselective 1,4-Conjugate Addition to Nitrodiene **19I**.[50,51]



Namboothiri and coworkers[52] reported the diastereoselective Morita-Baylis–Hillman reaction of carbonyl compounds with nitrodienes in the presence of stoichiometric amounts of *N*,*N*-dimethylamino pyridine (DMAP) (**Scheme 5.1.10**). This method allowed the addition of ethyl orthoformate **62** at the α- to the nitro group of nitrodiene **19I** affording α,β-bifunctionalized product **63**. Attempted screening of Lewis bases and solvents showed that DMAP and acetonitrile gave the highest yield and diastereoselectivity under optimized reaction conditions (85%, dr 100:0). The application of identical condition in the reaction of nitrodiene **19I** with methyl vinyl ketone (MVK, **64**) in the presence of stoichiometric amounts of imidazole using LiCl (50 mol%) as an additives gave Rauhut-Currier adduct **65** in poor yields (33%).[53]

Scheme 5.1.10 Diastereoselective Addition of Carbonyl Substrate to Nitrodiene **19I**.[52,53]

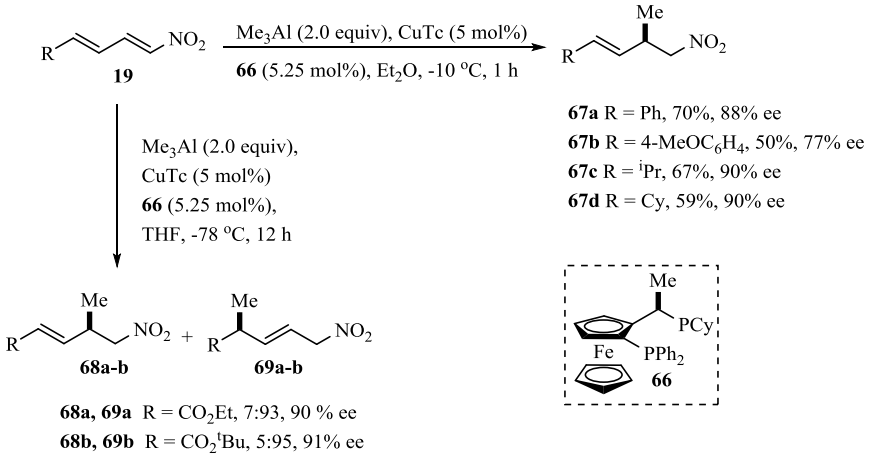


Despites these examples of enantioselective 1,4-addition reaction of aldehydes or ketones to nitrodienes, the analogous 1,4-addition reaction of organometallic reagents to nitrodienes has received relatively little attention. This deficiency in part may arise from the selectivity of the organometallic reagents towards 1,6-addition or the lack of suitable catalyst for asymmetric reaction. For examples, organocuprates preferred[54] or copper,[6-9] iron,[10, 11] nickel,[12] ruthenium,[13, 14] and iridium,[15, 16] catalyzed reaction of organometallic reagents with extended Michael substrate usually proceed through the 1,6-conjugate addition[14, 17] pathway.

Recently, Alexakis and coworkers reported the first and only example of copper catalyzed regio- and enantioselective 1,4- and 1,6-conjugate addition reaction of trialkylaluminium reagents to nitrodienes in the presence of chiral transition metal catalysts (**Scheme 5.1.11**).[55] The reaction of Me_3Al reagents with 1-nitro-4-phenyl-1,3-butandiene (**19I**) in the presence of catalytic amounts of copper(I) thiophen-2-carboxylate (CuTc, 5 mol%) and Josiphos catalyst **66** (5.25 mol%) gave 1,4-adduct **67** in good yield and good enantioselectivity (70%, 88% ee). Although, the presence of electron donating group at the *para*- position of the phenyl ring diminished the yield and enantioselectivity, the use of alkyl substituent's (e.g., isopropyl or cyclohexyl group) at the δ-position of the nitrodiene under identical reaction

conditions improved the yield and enantioselectivity (67%, 90% ee and 59%, 90% ee respectively).

Scheme 5.1.11 Enantioselective 1,4-Addition of Me_3Al to Nitrodiene **19**.[55]

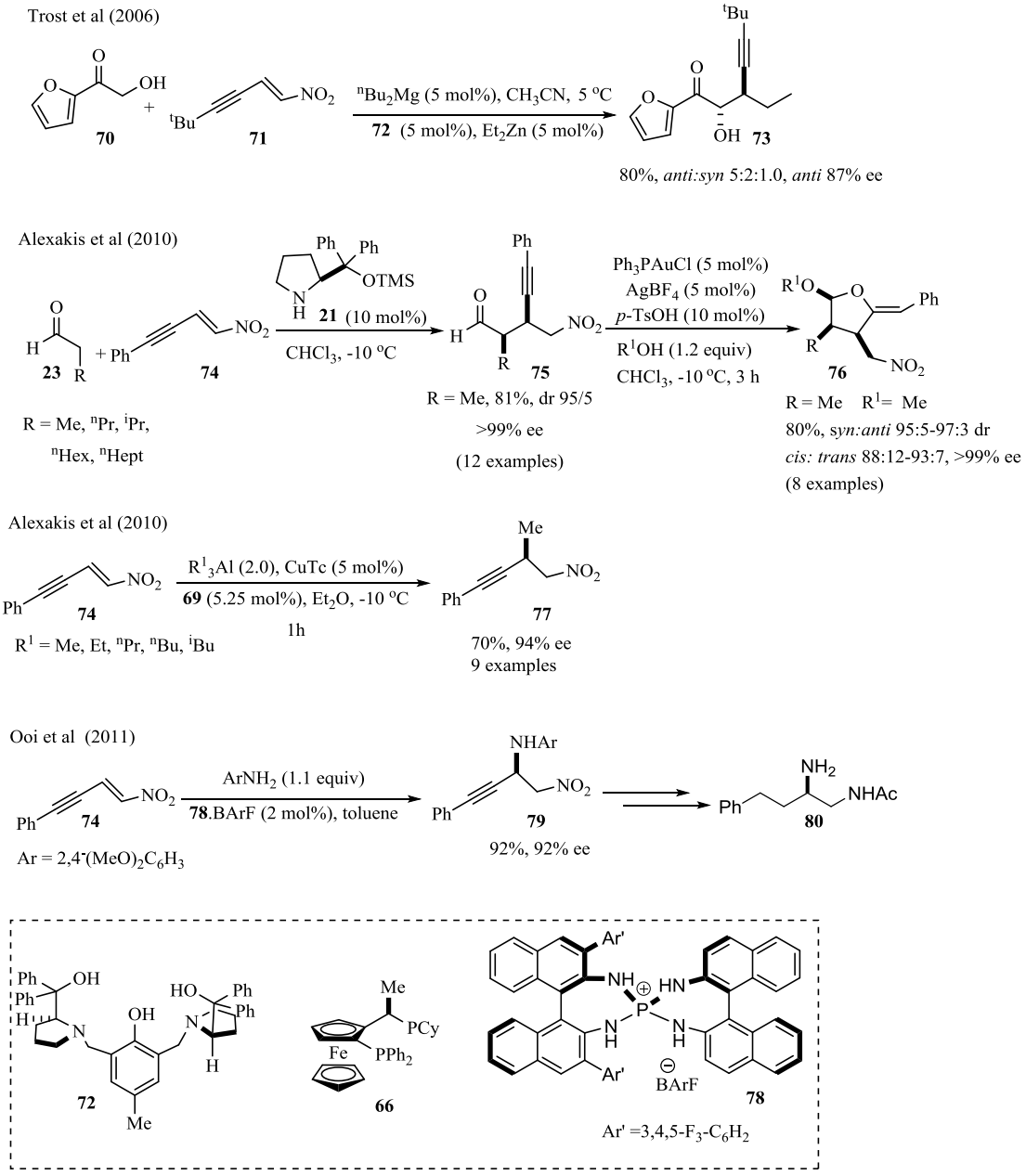


Surprisingly, the reaction of Me_3Al with functionalized nitrodiene (R = CO_2Et or $CO_2{}^tBu$) in the presence of catalytic amounts of CuTc gave 1,6-adduct with respect to nitro group in good yield and good enantioselectivity. This unusual addition of Me_3Al reagents to functionalized nitrodiene was rationalized due to the coordination of ferrocene based catalyst with the carbonyl group of the ester thereby activating the 1,6-position with respect to nitro group.

5.1.23 Conjugate Addition to Nitroenynes

Nitroenyne are highly attractive reactive synthon that undergo 1,4-conjugate addition reactions with nucleophilic species to give homopropargylic nitro compounds. The functional group transformations of the nitro[22] or alkynyl moiety[56] give synthetically important intermediates for the synthesis of complex organic molecules. 1,4-Conjugate addition of α-hydroxy ketones to nitroenynes catalyzed by chiral transition metal complex (**72**),[57] and chiral (*S*)-diphenylprolinol silyl ether **21**[35, 36, 58] catalyzed 1,4-addition of aldehyde to nitroenyne **71** and **74** were recently explored (**Scheme 5.1.12**). Enantioselective 1,4-conjugate addition of aldehyde **23** to nitroenyne **74** followed by gold catalyzed acetalization/cyclization in the presence of alcohol (methanol, ethanol or isopropanol) gave tetrahydrofuranyl ethers **76** in excellent yield and excellent enantioselectivity. Chiral ferrocene ligand **66** catalyzed enantioselective 1,4-addition of trialkylaluminium reagents[55] and chiral ionic Brønsted acid catalyzed enantioselective 1,4-addition of aniline based reagents[59] to nitroenyne **74** were recently explored. In both of these reactions, excellent yields and good enantioselectivity of the 1,4-adduct was achieved confirming the versatility of methodologies for the conjugate addition reactions. The absolute configuration of product **79** was determined by converting them into known *N*-monoacetyldiamine **80**.[60]

Scheme 5.1.12 Enantioselective 1,4-Addition of Nucleophiles to Nitroenyne. [35, 36, 55,58-60]



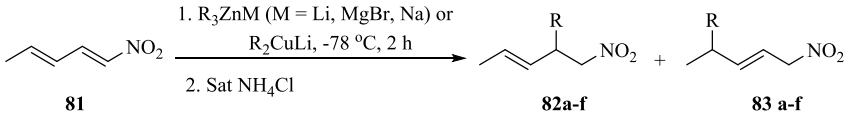
In summary, a large number of enantioselective 1,4-addition reactions of aldehydes or ketones to nitroalkenes, nitrodienes and nitroalkynes catalyze by proline,[33-36] bifunctional amine-thiourea derivatives,[37-41] cinchona alkaloids[42, 43] and aminoacids[44, 45] based organocatalysts are reported in the literature. Although the intermediates involved in reaction were not successfully isolated, mechanistic study for the reaction of these organocatalyst with nitrodiene suggested the participation of enamine[46] or enol[47] intermediate and was also supported by recent theoretical studies using DFT calculations. Despites notable successes in the enantioselective conjugate addition reactions of carbonyl substrates, only a few example on the regio- and enantioselective 1,4-conjugate addition of organometallic reagents[55] to nitrodiene was reported. This may be due to the less compatible nature of the reagents with the nitro-functional group or the lack of suitable catalysts for effecting the conjugate addition reaction with high regioselectivity. Organozinc and organozincate reagents by the virtue of their preparation and high compability with a large number of functional groups (e.g.; cyanide, esters) have long been considered as one of the effective reagents in the conjugate addition reactions in the presence or absence of transition metals or organocatalysts. Intriguingly, one example on Zn(II) catalyzed regioselective conjugate addition reaction of to the nitrodiene was reported in the literature.[51] Our interest lies in exploring the chemistry of organozincate reagents for the regioselective 1,4-conjugate addition to nitrodienes as a continuation of regioselective 1,4-addition to functionalized diene system employing organozincate reagents previously explored in our laboratory. Here in, we will thoroughly discuss the optimizing protocol for the regioselective 1,4-addition of organozincate reagents to the nitrodiene recently explored in our laboratory. A part of our result was recently published and reported in this dissertation with the permission from American Chemical Society.[61]

5.1.3 Results

5.1.31 Reaction of Triorganozincate Reagents with Nitrodienes

As a part of our research for exploring new methodologies for the regioselective 1,4-conjugate addition reaction of organozincate reagents to Michael substrates, the reaction of organozincate reagents with nitrodienes was investigated. A simple nitrodiene substrate, (*E*)-1-nitro-2,4-pentadiene (**81**) was chosen as test substance for our study. $^{n}Bu_3ZnLi$ reagent was prepared from the reaction of $^{n}BuLi$ (3.0 equiv) with flame dried zinc bromide (1.0 equiv) using Alexakis procedure[62] and employed for the reaction with nitrodiene **81**. Although, 1,4-conjugate addition was the favored process, a mixture of 1,4- and 1,6-adduct was observed in THF at -40 ^{o}C (**Table 5.1.1**; entry 1, 78%, regio 82:18). When the reaction was carried out at -78 ^{o}C in THF, the yield and regioselectivity was slightly better (entry 2). The reaction can also be carried out in non-coordinating solvents (i.e. CH_2Cl_2 or toluene in entry 3 and 4) but with diminished yield and slightly better regioselectivity. The application of magnesium zincates with nitrodiene **81** at lower temperature did not change the yield and regioselectivity of the conjugate addition products (entry 5). In all of these reactions, the 1,4-adduct was obtained as a major product. As expected, the reaction of $^{n}Bu_2CuLi$ or $^{n}BuCuCNLi$ with **81** at low temperature gave exclusively the 1,6-adduct (entries 6 and 7) although monoalkyl cuprates (i.e., RCuCNLi) gave slightly lower yield. Application of the less reactive Me_3ZnLi under identical reaction conditions gave good yield and better regioselectivity (entry 8). $^{i}PrMe_2ZnMgCl$ gave good yields of conjugate adduct but poor regioselectivity (entry 9, 78%, 1,4:1,6; 88:12). Although, the reaction of $^{t}Bu_3ZnLi$ with nitrodiene **81** in both coordinating (i.e. THF) and non-coordinating solvents (i.e., toluene) gave good yield of conjugate addition product, regioselectivity was poor (entries 10-12). Employment of $^{t}BuMe_2ZnLi$ in THF at lower temperature offered slightly better regioselectivity (entries 13-14).

Table 5.1.1 Regioselective 1,4-Addition of Organozincate/ Organocuprate Reagents to Nitrodiene **81**.[61]



81 **82a-f** **83 a-f**

a R = ^{n}Bu **b** R = Me **c** R = ^{i}Pr
d R = ^{t}Bu **e** R = ^{n}BuO **f** R = ^{n}PrS

entry	R_3ZnM/R_2CuLi[a]	solvent	temp °C (h)	% yield (**82+83**)[b]	regio (**82:83**)[c]
1	^{n}Bu$_3$ZnLi (1.0)	THF	-40 (12)[d]	78	82:18
2	^{n}Bu$_3$ZnLi (1.0)	THF	-78 (3)	81	84:16
3	^{n}Bu$_3$ZnLi (1.0)	CH_2Cl_2	-78 (3)	78	87:13
4	^{n}Bu$_3$ZnLi (1.0)	PhMe	-78 (3)	72	88:12
5	^{n}Bu$_3$ZnMgBr (1.0)	THF	-78 (12)[d]	74	78:22
6	^{n}Bu$_2$CuLi (1.5)	THF	-78 (12)[d]	77	0:100
7	^{n}BuCuCNLi (1.1)	THF	-78 (12)[d]	55	0:100
8	Me$_3$ZnLi (1.0)	THF	-78 (12)[d]	71	90:10
9	^{i}PrZnMe$_2$MgBr (1.0)	THF	-78 (12)[d]	78	88:12
10	^{t}Bu$_3$ZnLi (1.0)	THF	-40 (3)	80	50:50
11	^{t}Bu$_3$ZnLi (1.0)	THF	-78 (3)	72	56:44
12	^{t}Bu$_3$ZnLi (1.0)	PhMe	-78 (3)	71	55:45
13	^{t}BuZnMe$_2$Li (1.0)	THF	-78 (6)[d]	73	78:22
14	^{t}BuZnMe$_2$Li (1.0)	THF	-78 (3)	69	92:8
15	(^{n}BuO)$_3$ZnNa (1.0)	THF	-20 (12)[d]	81	100:0
16	(^{n}PrS)$_3$ZnNa (1.0)	THF	0-rt (1)	79	6:94
17	(^{n}PrS)$_3$ZnNa (1.0)	THF	-78 (3)	79	5:95

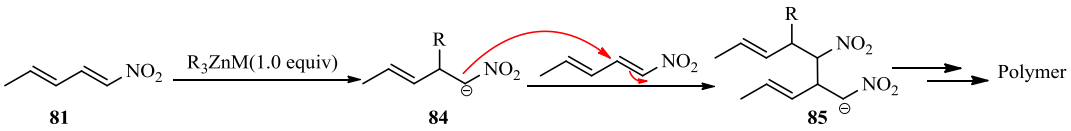
[a] $ZnBr_2$ was flame dried under vacuum before use for the preparation of organozincate reagents. [b] Yields are based upon isolated products purified by column chromatography. 5-10% of polymerized by-product was also characterized by ^{1}H and ^{13}C-NMR of the crude products. [c] Regio-isomeric ratio was determined from the ^{1}H NMR integration of vinyl hydrogen absorptions or peak heights of vinyl carbon absorptions in ^{13}C NMR. [d] Reagents were added at indicated temperatures and allowed to warm up to room temperature.

Surprisingly, the reaction of (^{n}BuO)$_3$ZnNa (prepared from the reaction of ^{n}BuONa (3.0 equiv) with zinc bromide (1.0 equiv)) with nitrodiene **81** gave excellent yield of 1,4-conjugate adduct. In this reaction, not even a trace amounts of 1,6-addition product was observed. The surprise participation of (^{n}BuO)$_3$ZnNa (1.0 equiv) as transferring ligand in the reaction prompted

us employing (^{n}PrS)$_3$ZnNa (1.0 equiv) for the reaction with nitrodiene **81**. However, in this reaction, 1,6-adduct was observed as major product along with minor 1,4-adduct (entries 16, 17).

In all of these reactions 5-10% of the polymerized byproduct was characterized by ^{1}H and ^{13}C-NMR of the crude products. The formation of the byproduct was expected to proceed via following mechanism.

Scheme 5.1.13 Proposed Mechanism for Polymerization of Nitrodiene.

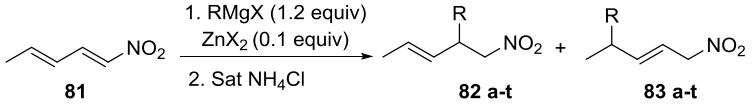


5.1.22 Catalytic Procedure in the Regioselective 1,4-Addition of Grignard Reagent to Nitrodiene 81.

The regioselective 1,4-addition reaction to nitrodiene employing stoichiometric amounts of triorganozincate reagents has two major limitation. Firstly, the 1,4-regioselectivity of the addition was poor to moderate in both coordinating and non-coordinating solvents. Secondly, only one equivalent of the reagent was used for the reaction while remaining two equivalent of reagents lost during the workup procedure which is cost inefficient while employing expensive organic ligand for the reactions. Hence, in an effort to control the 1,4-regioselectivity and reduce the amounts of organometallic reagents used for the reaction, a procedure catalytic in Zn(II) salt was designed. The controlled experiment involving the reaction of ^{n}BuMgCl (1.0 equiv) with nitrodiene **81** in the absence of Zn(II) salts gave moderate yields of conjugate adduct but with

poor regioselectivity (**Table 5.2**, entry 1). When the reaction of ^{n}BuMgCl (1.2 equiv) was carried out with nitrodiene **81** in the presence of catalytic amounts of zinc bromide (0.1 equiv) at -40 ^{o}C, good yield and good 1,4-regioselectivity was observed (entry 2). The application of ^{n}Bu, Me, ^{i}Pr or Bn- Grignard reagents in polar coordinating solvents (i.e., THF or Et_2O) gave good yields but moderate 1,4-regioselectivity (entries 2-3, 6-7) while the utilization of non-coordinating solvents such as CH_2Cl_2 or toluene enhanced the 1,4-regioselectivity (entries 4-5, 87% and 86 %, regio 91:9 and 92:8 respectively). Interestingly, the reaction of $PhCH_2MgBr$ in coordinating solvent (e.g., THF) at low temperature gave excellent yields and good 1,4-regioselectivity (entry 8, 77%, regio 95:5), while the reaction at higher temperature or in non-coordinating solvents (Et_2O or toluene) diminished the regioselectivity (entries 9-12, 72-89%, 1,4:1,6; 67:33-82:18). Allyl Grignard reagents gave good yields and good regioselectivity in both coordinating (e.g., THF or Et_2O) and non-coordinating (e.g., CH_2Cl_2) solvents (entries 13-15). Our encouraging results on regioselective 1,4-conjugate addition reactions of alkyl Grignard reagents with nitrodiene **81** prompted us to test the reaction of aryl Grignard reagents with nitrodiene **81** in the presence of catalytic amounts on zinc(II) salts.The reaction of PhMgBr with nitrodiene **81** in Et_2O gave excellent yields of the conjugate adduct with moderate 1,4-regioselectivity (entry 16, 83%, 1,4:1,6; 80:20). The application of a non-coordinating solvent (e.g., CH_2Cl_2) or the use of $Zn(CN)_2$ as Zn(II) ion source under identical reaction conditions enhanced the yield and regioselectivity (entries 17 and 18, 77 vs 85%, **82g:83g**, 93:7 vs 98:2). Surprisingly, application of 1-naphthyl-, 4-$MeOC_6H_4$-, 4-$Me_2NC_6H_4$-, 5-(*N*-methylindolyl)-, 2-furyl-, 2-thionyl-, 2-(*N*-methylpyrrolyl)-, and ^{n}BuCH=CHMgBr using the procedure catalytic in Zn(II) salts in coordinating or non-coordinating solvents gave exclusive 1,4-conjugate addition products in excellent yields (entries 19-28, dr 100:0, 72-83%).

Table 5.1.2 1,4-Conjugate Addition of Grignard Reagent Catalyzed by Zn (II) Salts.[61]



81 82 a-t 83 a-t

a R = Bu **i** R = Ph **o** R = 2-furyl
b R = Me **j** R = 2-MeC_6H_4 **p** R = 2-thienyl
c R = ^{i}Pr **k** R = 1-naphthyl **q** R = 2-(1-methylpyrrolyl)
d R = ^{t}Bu **l** R = 4-$MeOC_6H_4$- **r** R =1-hexenyl
g R = Bn **m** R = 4-$Me_2NC_6H_4$- **s** R = ^{n}BuC≡ C-
h R = CH_2=$CHCH_2$- **n** R = 5-(*N*-methylindolyl)- **t** R = PhC≡C-

entry	R	ZnX_2[a]	solvent	temp ^{o}C (h)[b]	% yield (**82+83**)[c]	regio (**82:83**)[d]
1	^{n}Bu-	-	THF	-78 (3)	65	65:35
2	^{n}Bu-	$ZnBr_2$	THF	-40 (12)	81	88:12
3	^{n}Bu-	$ZnBr_2$	THF	-78 (2)	83	90:10
4	^{n}Bu-	$ZnBr_2$	CH_2Cl_2	-78 (2)	87	91:9
5	^{n}Bu-	$ZnBr_2$	PhMe	-78 (2)	86	92:8
6	Me-	$ZnBr_2$	THF	-78 (3)	75	91:9
7	^{i}Pr-	$ZnBr_2$	THF	-78 (3)	76	90:10
8	Bn-	$ZnBr_2$	THF	-78 (3)	77	95:5
9	Bn-	$ZnBr_2$	Et_2O	0 (12)	85	67:33
10	Bn-	$ZnBr_2$	Et_2O	-20 (12)	86	76:24
11	Bn-	$ZnBr_2$	Et_2O	-78 (3)	89	82:18
12	Bn-	$ZnBr_2$	PhMe	-78 (3)	72	78:22
13	CH_2=$CHCH_2$-	$ZnBr_2$	THF	-78 (2)	74	95:5
14	CH_2=$CHCH_2$-	$ZnBr_2$	Et_2O	-78 (3)	85	96:4
15	CH_2=$CHCH_2$-	$ZnBr_2$	CH_2Cl_2	-78 (3)	89	96:4
16	Ph-	$ZnBr_2$	Et_2O	-78 (12)	83	80:20
17	Ph-	$ZnBr_2$	CH_2Cl_2	-40 (3)	77	93:7
18	Ph-	$Zn(CN)_2$	CH_2Cl_2	-40 (3)	85	98:2
19	1-napthanyl-	$ZnBr_2$	Et_2O	-20 (12)	83	100:0
20	4-$MeOC_6H_4$-	$Zn(CN)_2$	CH_2Cl_2	-20 (12)	73	100:0
21	4-$Me_2NC_6H_4$-	$ZnBr_2$	THF: CH_2Cl_2[e]	-78 (12)	72	100:0
22	5-(*N*-methylindole)	$ZnBr_2$	Et_2O	-20 (12)	73	100:0
23	2-furyl-	$ZnBr_2$	Et_2O	0 (12)	70	100:0
24	2-furyl-	$ZnBr_2$	Et_2O	-40 (12)	83	100:0
25	2-thienyl-	$ZnBr_2$	Et_2O	0 (12)	75	100:0
26	2-thienyl-	$ZnBr_2$	Et_2O	-20 (12)	81	100:0
27	2-(*N*-methylpyrrol)	$ZnBr_2$	Et_2O: THF[f]	-20 (12)	79	100:0
28	^{n}BuCH=CH-	$ZnBr_2$	Et_2O	-78 (3)	83	100:0
29	^{n}BuC≡C-	$ZnBr_2$	Et_2O	-20 (12)	76	100:0
30	PhC≡C-	$ZnBr_2$	Et_2O	-20 (12)	87	72:28
31	PhC≡C-	$Zn(CN)_2$	Et_2O	-20 (12)	83	93:7

[a] $ZnBr_2$ was flame dried under vacuum prior to use for the reactions. [b] Reagents were added at indicated temperature and warmed to room temperature over the indicated time. [c] Yields are based upon isolated products purified by column chromatography. [d] Regioisomeric ratios were determined from the interigation of ^{1}H NMR absorption of vinyl hydrogens or peak height of the vinyl carbon absorptions in ^{13}C NMR spectrum. [e] THF:CH_2Cl_2 (1:1) was used. [f] Et_2O:THF (3:1) was used.

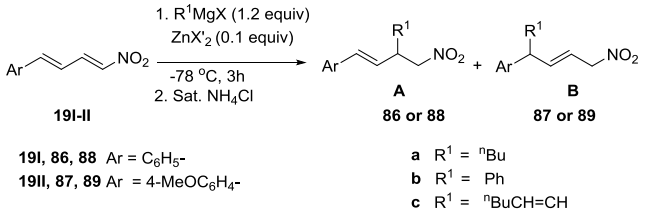
To our surprise alkynyl group which was regarded as a dummy ligand in our previous investiagation (Chapter II, Table 2.2, entry 4) was also successfully transferred to nitrodiene **81** when catalytic procedure was employed. Although, ^{n}BuC≡CMgBr gave exclusive 1,4 conjugate adduct in Et_2O (entry 29, 76%, **82q:83q**, 100:0), the more electron deficient PhC≡CMgBr gave corresponding products in good yields but poor regioselectivity (entry 30, 87%, **82q:83q**, 72:28) under identical reaction conditions. The reaction of PhC≡CMgBr in the presence of $Zn(CN)_2$ (0.1 equiv) with nitrodiene **81** however gave 1,4-adduct in excellent yield (entry 31, 83%, **82r:83r**, 93:7).

5.1.33 Substrate Scope of the Reactions

In an attempt to extend the substrate scope of the reactions, *(E)*-1-nitro-4-phenyl-1,3-butandiene (**19I**) and *(E)*-1-nitro-4-(4-methoxyphenyl)-1,3-butandiene (**19II**) were synthesized using literature procedure[9] and employed for the reaction with Grignard reagents using procedure catalytic in zinc(II) salts. The reaction of ^{n}BuMgCl (1.2 equiv) with **19I** in the presence of catalytic amounts of zinc cyanide (0.1 equiv) in both coordinating (i.e., THF) and non-coordinating solvents (i.e., CH_2Cl_2, toluene) was investigated. In all of these reactions, 1,4-adduct was observed in moderate yield and poor regioselectivity (**Table 5.3**, entries 1-3, 63-65%, 1,4:1,6; 78:22-80:20). The application of identical procedure for the reaction of PhMgCl (1.2 equiv) with **19I** in THF also gave moderate yield and poor regioselectivity (entry 4, 66%, 1,4:1,6; 60:40). The use of zinc cyanide as a source of Zn(II) ion in coordinating or non-coordinating solvents did not significantly change the yields and regioselectivity (entries 5-6). Although the reaction of ^{n}BuMgCl with **19II** gave conjugate addition product in good yields and poor regioselectivity (entry 7, 73%, 1,4:1,6; 78:22), application of PhMgCl under identical conditions exclusively gave 1,4-adduct in good yield (entry 8, 71%, 1,4:1,6; 100:0). Besides, vinyl Grignard

reagents also gave exclusively the 1,4-conjugate addition product in good yield (entry 9, 73%, 1,4:1,6; 100:0) under identical reaction conditions.

Table 5. 1.3. Zn(II) Salts Catalyzed 1,4-Conjugate Addition of Grignard Reagents to Aryl Nitrodiene. [61]



entry	nitrodiene	R-	ZnX_2	solvent	% yield[a] **A+B**	regio[b] **A:B**
1	**19I**	^{n}Bu-	$Zn(CN)_2$	THF	65	78:22
2	**19I**	^{n}Bu-	$Zn(CN)_2$	CH_2Cl_2	67	80:20
3	**19I**	^{n}Bu-	$Zn(CN)_2$	PhMe	63	78:22
4	**19I**	Ph-	$ZnBr_2$	THF	66	60:40
5	**19I**	Ph-	$Zn(CN)_2$	THF	77	65:35
6	**19I**	Ph-	$Zn(CN)_2$	PhMe	58	60:40
7	**19II**	^{n}Bu-	$Zn(CN)_2$	THF	73	78:22
8	**19II**	Ph-	$ZnBr_2$	THF	71	100:0
9	**19II**	^{n}BuCH=CH[c]	$ZnBr_2$	THF	73	100:0

[a] Yields are based upon isolated pure compounds after flash column chromatography. [b] Regioisomeric ratio was determined from the intrigation of ^{1}H NMR absorption of vinyl hydrogen or peak height of the vinyl carbon absorptions in ^{13}C NMR spectrum. [c] Vinyl Grignard reagent was prepared from the halogen metal exchange reactions of the corresponding vinyl iodide followed by reaction with $MgBr_2$.

5.1.4 Discussion

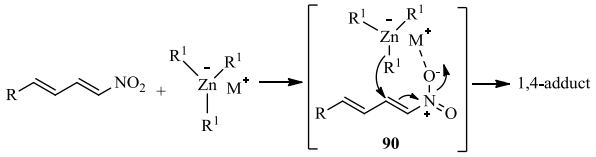
Nitrodienes are highly versatile reactive synthons for the synthesis of biologically important natural products[31, 32] and their synthetic intermediates. The presence of the nitro group at the terminal position of conjugated diene create unequal distribution of charge in the C=C bonds. This unequal distribution of electrophilicity in the C=C bonds of nitrodienes results in different rate of nucleophilic attack at 1,4- or 1,6-position which are reflected in the regioselectivity of the reaction.

In the conjugate addition reactions of carbon nucleophiles to nitrodienes, there is not a single catalyst of wide efficiency. For example proline,[33-36] bifunctional amine-thiourea derivatives,[37-41] cinchona alkaloid[42, 43] and aminoacid[44, 45] based organocatalysts have shown their versatility for the enantioselective 1,4-addition of carbonyl substrates with high efficiency while ferocene based catalyst[55] were the choice for the copper catalyzed enantioselective 1,4-addition of trialkylaluminium to nitrodine. The use of organometallic reagents for regio- and stereoselective 1,4-conjugate additions to nitrodienes is rather limited. A singular report on 1,4-additions of tri-organoaluminum reagents[55] to nitroalkenes was followed recently by a report for the regio- and enantioselective 1,4- or 1,6-conjugate addition reactions of trialkylaluminium reagents to nitrodienes employing catalytic amounts of Cu(I) salts and ferrocene based chiral catalysts. We explored an efficient method for the regioselective 1,4-conjugate addition reactions of Grignard reagents to nitrodienes in the presence of catalytic amounts of zinc(II) salts.

The precise identification of the species involved in the conjugate addition reactions has yet to be explored, however IR and NMR spectroscopic analysis of $LiZnMe_3$[63] and synthesis and characterization of first the magnesium *bis*-(tribenzylzincate) complex (i.e., $Mg(thf)_6[Zn(CH_2Ph)_3]_2$, **15**)[64] suggested the involvement of ion pairs in the organozincate

reactions. This result was further supported by the successful characterization of the zincate species generated in the reaction of Grignard reagents with stoichiometric and catalytic amounts of $ZnCl_2$ (vide supra, **Scheme 1.6** and **Figure 2.1**).[65] Their structural variations observed in the solution and solid state analyses of organozincate reagents suggested that the structure of organozincate reagents is more complex than that represented by the general molecular formula R_3ZnM.

Scheme 5.1.14. Proposed Mechanism for 1,4-Addition of Triorganozincates to Nitrodiene.



Although complex **90** has been invoked[66] to account for the tendency of organozinc reagents to undergo 1,4-addition to *α,β*-unsaturated carbonyl compounds in contrast to the 1,2-addition pathway of Grignard and organolithium reagents and could explain the preference for 1,4-selectivity, the model does not fully comport with our experimental data. Contrary to expectations, the 1,4:1,6-regioselectivity is relatively insensitive to solvent coordinating ability (for example, THF vs. CH_2Cl_2 or PhMe (Doner Numbers = 20-0): **Table 5.1.1**, entries 2 vs. 3-4, 11 vs. 12; **Table 5.1.2**, entries 3 vs. 4-5, 8 vs. 11-12, and 13 vs. 14-15) where a contact ion-pair (CIP)[65, 67] for the zincates in CH_2Cl_2 or PhMe should favor greater 1,4:1,6-selectivity and a solvent separation ion-pair (SSIP)[65, 67] in THF should induce lower selectivity.[61]

Calculations indicate that the d-orbitals on organo-Zn(II) species are low lying in comparison[66, 68] to those of organocuprates (e.g., R_2CuM) so that the organo ligands act as the nucleophiles in the former while the Cu-atom acts as the nucleophile in the latter. The zinc reagents follow a pathway of carbozincation[66] while the cuprate reagents undergo oxidative

addition and favor 1,6-addition via σ-π-allyl-σ-Cu(III) rearrangements. The preference for zincate 1,4-addition could be rationalized by differential charge density or orbital coefficient magnitudes at the *γ*- and *δ*- positions which correctly rationalizes regiochemistry in FMO models. [61,69]

Simple semi-empirical PM3 calculations using a MacSpartan program give charge differences between C2 and C4 [compound Δ(C2-C4): **81** (+ 0.125627), **19I** (+ 0.078615) and **19II** (+ 0.070690)] and orbital coefficient differences [compound Δ(C2-C4): **81** (+ 0.7419), **19I** (+ 0.00254) and **19II** (+ 0.00201)] that mirror the observed 1,4:1,6-regioselectivity trends with aryl-substituted nitrodienes giving lower regioselectivity.[61] Charge density considerations also appear consistent with the 1,6-preference of $(^{n}PrS)_3ZnNa$; and 1,4-preference of $(^{n}BuO)_3ZnNa$ (Table 2, entries 16-17) in line with HSAB considerations.[69] This calculation correctly predict lower 1,4:1,6-regioselectivity for the aryl substituted nitro dienes **19I** and **19II**. As we did not find a general trend for the regioselective conjugate addition to nitrodiene, temperature and solvent play some role for controlling the regioselectivity.[61] However, several factors including types of electrophiles and nucleophiles, rate of reagent additions are also suggested to control the regioselectivity.

5.1.5 Conclusion

In summary, we developed a new methodology for the regioselective 1,4-conjugate addition reaction of Grignard reagents to nitrodienes employing a procedure catalytic in Zn(II) salts but in the absence of Cu(I) salts. All of the tested reactions were completed in a short time even at low temperature signifying the high reactivity of nitrodienes toward conjugate addition reactions. Control experiments confirmed that regioselectivity was indeed controlled by zinc (II) salts. The method is highly 1,4-regioselective for δ-alkyl substituted nitrodiene **81** showing excellent 1,4-selectivity for alkyl (90:10 to 92:8), benzyl (82:18 to 95:5), allyl (95:5 to 96:4), and alkynyl (93:7 to 100:0) Grignard reagents, while displaying exclusive to nearly exclusive 1,4-selectivity for aryl (98:2 to 100:0), heteroaryl (100:0) and vinyl (100:0) Grignard reagents. Although there are no uniform patterns, choice of solvent, Zn(II) salt and reaction temperature can be manipulated to increase 1,4-regioselectivity in those cases where initial experimenation led to 1,4:1,6-ratios below 90:10. δ-Substituted aryl nitrodienes **19I** and **19II** genearally display reduced 1,4-selectivity, although a 4-methoxyphenyl substituent (i.e., **19II**) did afford exclussive 1,4-selectivity with phenyl and alkenyl Grignard reagents. The scope of the method was also expended to heteroatom ligands wherein alkoxyzincate reagents gave exclusive 1,4-addition and alkylthiolatozincates gave high 1,6-selectivity (95:5). The conjugate addition of alkynyl and heteroatom ligands are particularly challanging for Cu(I) salts. To the best of our knowledge, this is the first example for the involvement of organozincate reagents generated in situ from corresponding Grignard reagents for the regioselective 1,4-conjugate addition reactions to nitrodienes. Detailed mechanistic study of the methodology invokes the isolation and characterization of intermediates involved in the reaction and theoretical studies using *ab-initio* calculations.

5. 2. 1,4-CONJUGATE ADDITION REACTIONS OF ORGANOZINCATE REAGENTS TO THIODIENOATES.

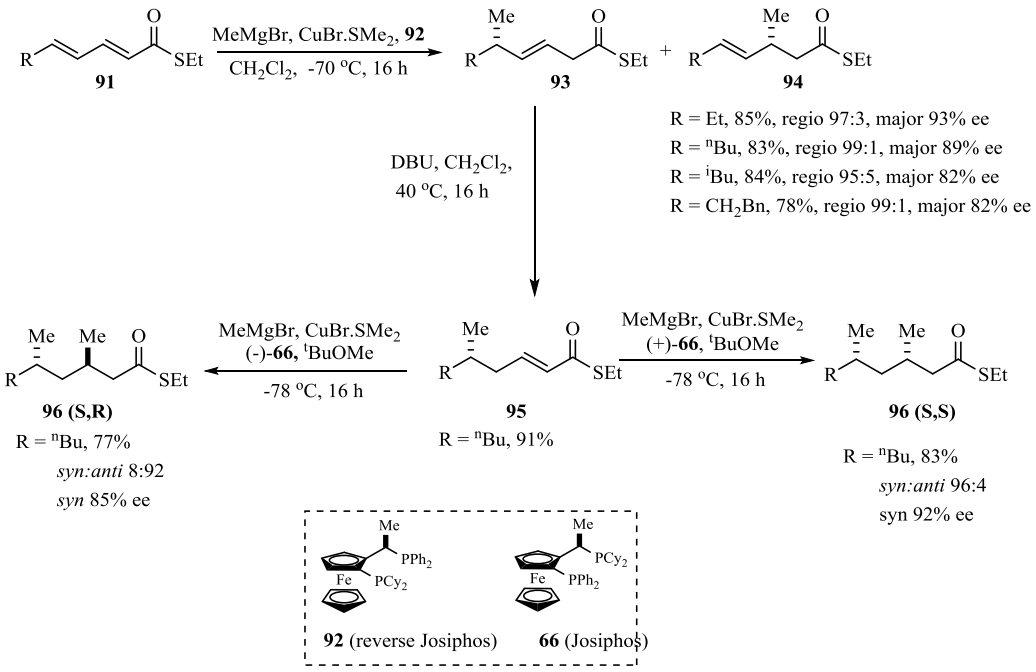
5.2.1 Introduction

As a part of our continued effort to develop new and general methodology for the regioselective conjugate addition reaction of Grignard reagents to Michael substrate, we already reported a general and efficient procedure for the (a) regio- and diastereoselective cyclopropanation reactions of organozincate reagents with functionalized epoxides and γ-haloenoates (for details; see chapter 2) and (b) regioselective 1,4-conjugate addition of the organozincate reagents to $\alpha,\beta,\gamma,\delta$-unsaturated nitrodienes (chapter 5.1). The great success in the above systems encouraged us to explore new methodology for the regioselective 1,4-conjugate addition of Grignard reagents to other extended Michael substrate. We first investigated the reaction of Grignard reagents with $\alpha,\beta,\gamma,\delta$-unsaturated thioesters in the presence catalytic amounts of Zn(II) salts. $\alpha,\beta,\gamma,\delta$-Unsaturated thioesters are highly reactive extended Michael substrates and are sulfur analogues of sorbate esters. The reactivity of these compounds with organometallic reagents and other nucleophilic species however is close to conjugated ketones rather than the corresponding esters. Regio- and stereoselective 1,4-conjugate addition of organometallic reagents to thiodienoates is barely reported in the literature. The development of such a regioselective protocol if successfully exploited will expand the scope of conjugate addition reactions.

The conjugation of functional groups with α,β-unsaturation generally shifted the reactivity of the functional group in the π-system. The second extension of conjugation further propagated the electronic effect to the δ-position. The reaction of nucleophilic reagents with conjugated Michael substrates usually give selectivity between 1,4- vs 1,6- sites. Yamamoto and coworkers[7] reported a new methodology employing fine tuning copper reagents for the

regioselective 1,4- or 1,6-conjugate addition reactions with linear dienoates. Naf and coworkers[6] reported the first example on 1,6-regioselective conjugate addition reactions of lithium di-*cis*-1-heptenylcuprate to ethyl and methyl *trans*-2,4-pentadienoate affording exclusively 3,6-diolefinic esters. In 2007, Jørgensen and coworkers[5] reported the organocatalytic asymmetric conjugate addition (ACA) reaction of β-ketoesters and glycine imines to the δ-substituted dienones and dienoates in high yield and high enantioselectivity. Feringa and coworkers[8] subsequently reported the first ACA reaction of Grignard reagents with dienoates and thiodieonates in the presence of catalytic amounts of copper salts and chiral Josiphos ligands (**Scheme 5.1.2**). The conjugate addition reaction of Grignard reagents to thiodienoates **91** in the presence of catalytic amounts of $CuBr.SMe_2$ and Joshipos (**66**) or reversed Josiphos (**92**) ligand gave 1,6-adduct in good yield, regio- and enantioselectivity. Control experiments confirmed that the catalytic system was essential for achieving high regio- and enantioselectivity since the absence of catalyst offered a mixture of 1,4- and 1,6-addition products. The reversed Josiphos **92** catalyzed 1,6-conjugate addition reactions of organocuprate reagents to **91** followed by DBU catalyzed alkene isomerization and a second conjugate addition of organocuprate reagents in the presence of Josiphos catalyst **66** gave both *syn*- and *anti*-1,3-dimethyldeoxypropionate **96** in excellent yields, regio- and enantioselectivity. The synthetic versatility of the newly developed methodology was illustrated by the successful application of the methodology for the total synthesis of sulfonated alkenes isolated from *Echinus Temnopleurus hardwickii*.[70]

Scheme 5.2.1 Regio- and Enantioselective Synthesis of *syn*- and *anti*-1,3-Dimethyl deoxypropionate.[8]

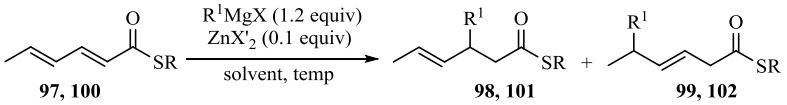


Only one example for the regioselective 1,4-conjugate addition reaction of organometallic reagents to conjugated thiodienoates was reported in the literature.[9] In order to shed a light into the methodology, we investigated the regioselective 1,4-addition of Grignard reagents to conjugated thiodienoates in the presence of catalytic amounts of zinc(II) salts. To the best of our knowledge, this is the first report for the introduction of organozincate reagents for the regioselective conjugate addition reaction to thiodieonates. The preliminary results explored in our lab will be discussed in the following section of this chapter.

5.2.2 Results and Discussion

We began our investigation employing the optimized conditions for the regioselective 1,4-addition reaction of Grignard reagents to nitrodiene in the presence of catalytic amount of zinc salts (vide supra, chapter 5.1) for the conjugated thiodieonates **97** and **100**. Our preliminary results showed that the reaction of ^{n}BuMgCl (1.2 equiv) with conjugated thiodieonates **97** in the presence of catalytic amounts of zinc bromide (0.1 equiv) at -78 ^{o}C in a polar coordinating solvent (i.e., THF) gave 1,4-conjugate addition products in good yields (**Table 5.2.1** entry 1, 67%, 1,4:1,6; 100:0). The reaction at higher temperature (-20 ^{o}C) enhanced the yield of 1,4-adduct with similar regioselectivity (entry 2, 76 %, regio; 100:0). The change of solvent from THF to Et_2O offered similar regioselectivity but with slightly higher chemical yield (entry 3, 82%, 1,4 vs 1,6; 100:0). The reaction ^{i}PrMgBr and ^{t}BuMgBr using procedure catalytic in $ZnBr_2$ with **100** although gave conjugate addition products in good yield, the regioselectivity was quite poor (entries 4 and 5, 73% vs 79, 1,4:1,6; 87:13 vs 73:27). The reaction of PhMgBr (1.2 equiv) gave exclusive 1,4-adduct in good yield (entry 6, 78%, regio 1,4 vs 1,6; 100:0). In the later reaction, $Zn(CN)_2$ was employed as catalyst as PhMgBr gave minimum amounts of coupling products (*vide supra*, chapter II, Table 2.7). The successful transfer of the phenyl group to the thiodienoates **97** prompted us to test the reaction of electron rich aryl Grignard reagents in the presence of catalytic amounts of zinc salts. 4-$Me_2NC_6H_4MgBr$ and 2-$MeOC_6H_4MgBr$ with **100** in the presence of catalytic amounts of Zn(II) salts also gave exclusive 1,4-adduct in moderate yield (entries 7 and 8 respectively).

Table 5.2.1 Regioselective 1,4-Conjugate Addition Reaction of Organozincate Reagents to Thiodieonate **97** and **100**.

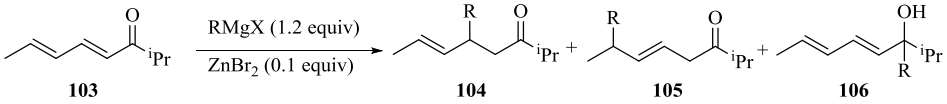


entry	SM	R^1MgX	ZnX_2	solvent	temp ^oC (h)[a]	% yield (**A**+**B**)[c]	regio (**A**:**B**)[b]
1	**97**	^{n}BuMgCl	$ZnBr_2$	THF	-78 (12)	67	100:0
2	**97**	^{n}BuMgCl	$ZnBr_2$	THF	-20 (12)	76	100:0
3	**97**	^{n}BuMgCl	$ZnBr_2$	Et_2O	-78 (12)	82	100:0
4	**100**	^{i}PrMgBr	$ZnBr_2$	Et_2O	-78(12)	73	87:13
5	**100**	^{t}BuMgBr	$ZnBr_2$	Et_2O	-78(12)	79	73:27
6	**97**	PhMgBr	$Zn(CN)_2$	Et_2O	-20 (12)	78	100:0
7	**100**	4-$Me_2NC_6H_4$-MgBr	$Zn(CN)_2$	THF	-20 (12)	59	100:0
8	**100**	2-$MeOC_6H_4$-MgBr	$ZnBr_2$	Et_2O	-20 (12)	51	100:0

[a] Reagents were added at indicated temperature and warmed to room temperature over the indicated time. [b] Regio isomeric ratio was determined from the ^{1}H-NMR integration of vinyl hydrogen absorptions or peak height of ^{13}C-absorptions of olefinic carbon. [c] Yields are based on the pure compounds isolated after flash column chromatography.

As a proof of concept, the 1,4-conjugate addition reaction of Grignard reagents to ketodiene in the presence of catalytic amounts of $ZnBr_2$ was also investigated in our laboratory. For this study (*2E,4E*) 1-methylethyl hexadienyl ketone **103** was chosen as test substrate for the conjugate addition reaction. Control experiment involving the reaction of ^{n}BuMgCl with ketodiene **103** in the absence of $ZnBr_2$ gave a mixture of 1,2- and 1,4-addition products (1:1) while the presence of Zn(II) catalayst exclusively gave the 1,4-adduct (**Table 5.2.2**, entries 1 and 2). Conducting the reaction in lower temperature also offered similar yield and similar regioselectivity (entry 3). The application of ^{i}PrMgBr and PhMgBr under identical conditions gave the mixture of 1,4-adduct and 1,2-adduct (entries 4 and 5 respectively).

Table 5.2.2 $ZnBr_2$ Catalyzed Regioselective 1,4-Addition of Grignard Reagents to Ketodiene.



103 **104** **105** **106**

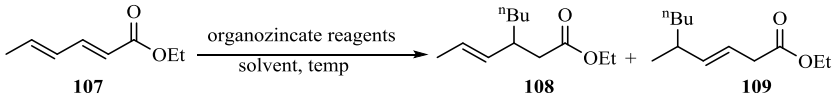
a R = ^{n}Bu **b** R = ^{i}Pr **c** R = Ph

entry	RMgX	catalyst (equiv)	solvent	temp ^{o}C (h) [a]	**104:105:106** [b]	% yield **104** [c]
1	^{n}BuMgCl	-	THF	-20 (1.5)	63:7:30	54
2	^{n}BuMgCl	$ZnBr_2$ (0.1)	THF	-20 (1.5)	87:4:09	73
3	^{n}BuMgCl	$ZnBr_2$ (0.1)	THF	-78 (3)	93:3:4	88
4	^{i}PrMgCl	$ZnBr_2$ (0.1)	THF	-78 (3)	80:16:4	77
5	PhMgCl	$ZnBr_2$ (0.1)	THF	-78 (3)	70:0:30	61

[a] Reagents were added at indicated temperature and warmed to 0 ^{o}C and quenched at that temperature over indicated time. [b] Regio isomeric ratio was determined from the intrigation of ^{1}H-NMR absorption of vinyl hydrogen or peak height of ^{13}C-absorptions of olefinic carbon. [c] Yields are based on the pure compounds isolated after flash column chromatography.

On the other hand, attempted conjugate addition reaction of organozincate reagents to (*2E, 4E*) ethyl hexadienoate (**107**) failed under identical reaction conditions (**Table 5.2.3**) although a literature report for the enantioselective 1,6-conjugate addition reactions of organocopper reagents to (*2E, 4E*) ethyl hexadionate (**107**) exist.[7]

Table 5.2.3 1,4-Conjugate Addition of Organozincate Reagents to Ethyl Sorbate.



107 **108** **109**

entry	reagents	ZnX_2 (equiv)	solvent	temp ^oC (h)[a]	product
1	^nBuMgCl (1.2),	$ZnBr_2$ (0.1)	THF	-78 (12)	mess[b]
2	$^nBu_3ZnLi$ (1.0)[c]	-	THF	-20 (12)	mess[b]
3	$^nBu_3ZnLi$ (1.0) $NiCl_2$ (0.1)[c]	-	THF	-78 (12)	mess[b]
4	$^nBu_3ZnLi$ (1.0),[c] $Ni(acac)_2$ (0.1)	-	THF	-78 (12)	mess[b]
5	^nBuMgCl (1.2), $Ni(acac)_2$ (0.1)	$ZnBr_2$ (0.1),	CH_2Cl_2	-40 (12)	SM
6	$^nBu_3ZnLi$ (2.0)[c], $Ni(acac)_2$ (0.1)	-	THF	-40 (12)	SM

[a] Reagents were added at indicated temperature and warmed up to room temperature over the indicated time. [b] Column inseparable mixture of five esters were confirmed by GC/MS and ^1H and ^{13}C NMR analysis of the crude product. [c] $^nBu_3ZnLi$ was synthesized at 0 ^oC.

5.23 Conclusion

Functionalized conjugated dienes are versatile synthons for the synthesis of large numbers of synthetic intermediates. The regio- and enantioselective 1,4-conjugate addition of organometallic reagents to these substrates is restricted to few *α,β,γ,δ*-unsaturated ketones, esters and thioesters. Our investigation showed that *n*-butyl, *iso*-propyl, *tert*-butyl, phenyl, 4-$Me_2NC_6H_4$- and 2-$MeOC_6H_4$- Grignard reagents can undergo facile 1,4-conjugate addition to *α,β,γ,δ*- unsaturated thioesters **97** and **100** in the presence of catalytic amounts of zinc(II) salts affording 1,4-adduct in good yields. The reaction can also be used for the 1,4-conjugate addition to ketodiene **103** under identical conditions.

Experimental

Some of the experimental procedure and IR, GC/MS and NMR data used for this chapter of the dissertation was recently published and reported with the permission from American Chemical Society.[61]

General: NMR spectra were recorded as $CDCl_3$ or C_6D_6 solutions on a 300 or 500 MHz NMR instrument. The ^1H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to $CHCl_3$ (δ = 7.28) as internal standard. The ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) and referenced with respect to the $CDCl_3$ signal (triplet, centerline δ = 77.0 ppm). Infrared (IR) spectra were recorded as neat samples (liquid films on NaCl plates). Gas chromatography-mass spectrometry measurements were performed on a GC coupled to a quadruple detector at 70 eV. Analytical thin layer chromatography (TLC) was performed on silica gel plates, 200 μ mesh with F_{254} indicator. Visualization was accomplished by UV light (254 nm), and 10% ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 230-400 mess silica. The yields were based upon isolated products purified by column chromatography.

Materials: Anhydrous tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were dried over molecular sieves and used for the reactions. ^{n}BuLi (2.5 M in hexane), MeLi (1.6 M in Et_2O), ^{t}BuLi (2.0 M in pentane) were commercially available and titrated using *sec*-butyl alcohol and 1,10-phenanthroline monohydrate in THF. ^{n}BuMgCl (2.50 M in THF), MeMgCl (3.0 M in Et_2O), ^{i}PrMgBr (2.0 M in Et_2O), and PhMgCl (2.80 M in Et_2O) were commercially available and titrated using menthol and 1,10-phenanthroline monohydrate in THF.[71] Benzyl bromide, 1-bromonapthalene, *N*,*N*-dimethyl-4-bromoaniline, 4-iodoanisole, 5-iodoindole, furan, thiophene,

N-methyl pyrrole, 1-hexyne, phenylacetylene, *n*-butyl alcohol, *n*-propyl thiol and 1,2-dibromoethane ($BrCH_2CH_2Br$) were commercially available and used for the reaction without purification. Zincate reagents were synthesized by the reactions of organolithium or organomagnesium reagents with commercially available ZnX_2 (X = Br, Cl, CN). All glassware was flamed-dried under high vacuum and purged with argon and then cooled under a dry nitrogen atmosphere. Low temperature baths (up to -78 ^oC) were prepared using thermoflasks with dry ice-*iso*-propanol slush bath mixtures or ice-NaCl (-23 ^oC) mixture. All reactions were conducted under a positive, dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

Method A: Synthesis of Grignard Reagent from Aryl halides. Aryl Grignard reagents that are not commercially available were synthesized in situ by using a literature procedure[72] from the corresponding aryl halides. To the magnesium (192 mg) in THF (5.0 mL) was added catalytic amount of iodide (15 mg) under argon at 50 ^oC. Then a solution of aryl halide (2.0 mmol in 5.0 mL THF) was added dropwise. After the addition was complete, the reaction mixture was stirred for an additional 30 minutes at room temperature and employed for the reaction using general procedure **A**.

Method B: Synthesis of Grignard Reagent from Heteroaryl Compound.[73] To the mixture of heteroaryl compound (2.0 mmol) and TMEDA (2.0 mmol) in THF/Et_2O (3.0 mL) at 0 ^oC under argon was added *n*-BuLi (0.80 mL, 2.50 M in hexane, 2.0 mmol) dropwise with continuous stirring. Then the resulting mixture was warmed to room temperature and stirred for 2 hours at room temperature. In the separate flask, $MgBr_2$ was prepared in situ by the reaction of 1,2-dibromoethane ($BrCH_2CH_2Br$, 2.0 mmol) with magnesium (51 mg, 2.1 mmol) in Et_2O and stirred the mixture for 15 minutes at room temperature.[73] Then $MgBr_2$ was transferred to the lithium

reagent containing flask via cannula under argon at 0 ^{o}C, stirred for additional 30 min at that temperature before used for the reaction using general procedure A.

Method C: Synthesis of Grignard Reagent from Halogen Metal Exchange. The halogen metal exchange reaction of aryl iodide was carried out using the literature procedure. To the solution of aryl iodide (2.0 mmol) in THF (3.0 mL) under argon at 0 ^{o}C was added ^{i}PrMgBr (0.78 mL, 2.0 M in Et_2O, 1.5 mmol) at -10 ^{o}C and the mixture was stirred for one hour at that temperature. The magnesium reagents thus prepared was next used for the further reaction using general procedure B. On the other hand, vinyl Grignard reagents were prepared by the iodine-lithium exchange reactions of vinyl iodide with ^{n}BuLi as described below. To the solution of vinyl iodide (1.0 equiv) was added ^{n}BuLi (1.0 equiv) in Et_2O at -78 ^{o}C under argon and stirred for 5 minutes at that temperature. The reaction flask was warmed to -30 ^{o}C bath and the solution of $MgBr_2$ in Et_2O (prepared in situ by the reaction of 1,2-dibromoethane (1.1 equiv) with magnesium (1.2 equiv) in Et_2O) was added at -30 ^{o}C via cannula under argon. The resulting reaction mixture was stirred for additional 30 mins at that temperature before employing for the reaction using general procedure A.

General Procedure A: Reaction of Trialkylzincate (R_3ZnM) with Nitrodiene. To the flame dried $ZnBr_2$ (225 mg, 1.0 mmol) in THF (4.0 mL) under argon was added alkyllithium or alkyl magnesium halide (3.0 mmol) and the reaction mixture was stirred for 30 minutes at 0 ^{o}C. The reaction flash was cooled to -78 ^{o}C bath and nitrodiene (1.0 mmol) was added on it and the resulting mixture was stirred for 3-12 hours at indicated temperature. The reaction mixture was quenched with saturated NH_4Cl (5.0 mL), filtered and the filtrate was extracted with Et_2O (3 x 10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and

then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (10-20 % CH_2Cl_2:petroleum ether).

General Procedure B: Zinc(II) salts Catalyzed Reaction of Grignard Reagents with Nitrodienes. To the mixture of dry ZnX_2 (X = Br, CN; 0.1 mmol) and nitrodiene (1.0 mmol) in THF or Et_2O or CH_2Cl_2 or toluene (4.0 mL) was added Grignard reagent (1.2 mmol) at -78 ^oC under argon and the resulting mixture was stirred for 2-12 hours at indicated temperature. The reaction was quenched with saturated aqueous NH_4Cl (5.0 mL), filtered and the filtrate was extracted with Et_2O (3 x 10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10-20%, CH_2Cl_2:petroleum ether).

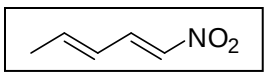
General Procedure C: Reaction of Organocuprate Reagents with Nitrodiene. To the solution of LiCl (85 mg, 2.0 mmol) and CuCN (89 mg, 1.0 mmol) in dry THF (3.0 mL) was added organolithium reagent (2.0 mmol) under argon at -78 ^oC and the resulting mixture was stirred for 45 mins at that temperature. To this solution, nitrodiene (1.0 mmol in 2.0 mL THF) was added at -78 ^oC and the resulting mixture was stirred for 12 hours with slightly warming to room temperature. The reaction mixture was quenched with saturated NH_4Cl (5.0 mL), diluted with water (10.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic phase was washed subsequently with brine (10.0 mL) and water (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether).

General Procedure D: Synthesis of *2E, 4E*-Nitrodiene. Nitrodiene was synthesized by using the slight modification of literature procedure.[55] To a slurry of $LiAlH_4$ (0.1 equiv) in dry THF (5.0 mL/mmol) was added nitromethane (5.0 equiv) at 0 °C. After 30 min, α,β-unsaturated aldehyde

(1.0 equiv) was added in one portion at 0 °C. The mixture was stirred for 14 hours at that temperature. The reaction mixture was quenched with HCl (1N) and diluted with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic phase was washed subsequently with brine and water then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography gave orange color oil which was purified using flash column chromatography (silica, 3-5% EtOAc:petroleum ether, v/v).

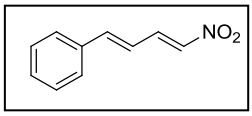
Next, to a freshly prepared nitro-alcohol solution (1.0 equiv) in dry CH_2Cl_2 (3.0 mL/mmol) was added trifluoroacetic anhydride (TFA, 1.05 equiv) at -40 °C and the resulting reaction mixture was stirred for 15 minutes at that temperature. Next, Et_3N (2.1 equiv) was added on it and the reaction mixture was then allowed to warm at room temperature over 12 hours before quenching with water. The reaction mixture was extracted with CH_2Cl_2, organic phase was washed subsequently with brine and water then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography. Then the resulting oil/solid was purified by a flash column chromatography (silica, 3-5% EtOAc:petroleum ether, v/v).

(2E,4E) **1-Nitropentadiene (81).**[55] Employing general procedure D and using crotonaldehyde



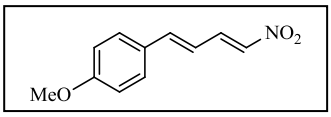
(2.1 g, 30.0 mmol), $LiAlH_4$ (114 mg, 3.0 mmol), nitromethane (8.2 mL, 150.0 mmol), TFA (4.4 mL, 31.5 mmol), Et_3N (8.8 mL, 63.0 mmol) after flash column chromatography on silica gel (10-15% CH_2Cl_2:petroleum ether, v/v) gave pure *2E,4E*-1-nitropentadiene **81**(1.83 g, 54%) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.95 (d, J = 6.9 Hz, 3H), 6.22 (t, J = 14.2 Hz, 1H), 6.46 (dt, J = 13.7, 6.8 Hz, 1H), 7.07 (d, J = 13.3 Hz, 1H), 7.57 (t, J = 12.8 Hz, 1H); ^{13}CNMR ($CDCl_3$, 125 Hz) δ 19.3, 124.7, 137.4, 139.3, 146.2.

(2E,4E) **1-Nitro-4-phenylbutadiene (19I).**[74] Employing general procedure D and using



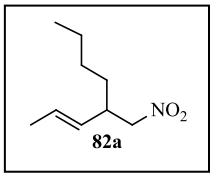
cinnamldehyde (3.96 g, 30.0 mmol), $LiAlH_4$ (114 mg, 3.0 mmol), nitromethane (8.2 mL, 150.0 mmol), TFA (4.4 mL, 31.5 mmol), Et_3N (8.8 mL, 63.0 mmol) after flash column chromatography (silica 10-15% CH_2Cl_2:petroleum ether, v/v) gave pure (*2E,4E)*-1-nitro-4-phenylbutadiene **19I** (3.57 g, 68%) as pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 Hz) δ 6.68 (dd, J = 4.2. 11.5 Hz, 1H), 7.12 (d, J = 15.1 Hz, 1H), 7.23 (d, J = 12.9 Hz, 1H), 7.38-7.59 (m, 4H), 7.75 (t, J = 12.4 Hz, 1H), 8.0 (J = 13.8 Hz, 1H); ^{13}CNMR ($CDCl_3$, 125 Hz) δ 127.7, 128.9, 129.0, 129.3, 129.9, 130.3, 132.1, 135.0, 137.0, 138.5, 139.0, 139.1.

(2E,4E) **1-Nitro-4-(4-methoxyphenyl)-butadiene (19II).**[35] Employing general procedure D and



using 4-methoxycinnamldehyde (1.62 g, 10.0 mmol), $LiAlH_4$ (38 mg, 1.0 mmol), nitromethane (2.8 mL, 50.0 mmol), TFA (1.50 mL, 10.6 mmol), Et_3N (3.03 mL, 30.0 mmol) after flash column chromatography (silica, 20-25% CH_2Cl_2:petroleum ether, v/v) gave **19II** (1.29 g, 63%) as pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 Hz) δ 3.87 (s, 3H), 6.74 (dd, J = 6.4, 12.6 Hz, 1H), 6.92-6.96 (m, 2H), 7.09-7.25 (m, 2H), 7.46-7.50 (m, 2H), 7.79 (t, J = 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 55.5, 114.5, 118.4, 128.0, 129.5, 137.6, 139.9, 146.0, 161.5.

(E) **2-(1-Propene)-1-nitrohexane (82a).** Employing general procedure B and using nitrodiene

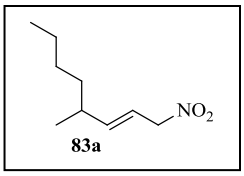


82a

(113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ^{n}BuMgCl (0.48 mL in THF, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2 in petroleum ether, v/v) gave the mixture of **82a** and **83a** as a colorless oil (139 mg, 81%, regio, 90:10). The application of ^{n}Bu_3ZnLi gave 133 mg, 78 %, regio 82:18 while the use of ^{n}$Bu_3ZnMgCl$ gave 127 mg, 74%, regio 78:22: IR (neat) 2960 (s), 2932 (s), 2861 (s), 1555 (s), 1434 (s), 1380 (s), 967 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90

(t, *J* = 6.9 Hz, 3H), 1.22-1.42 (m, 6H), 1.68 (d, *J* = 6.4 Hz, 3H), 2.77-2.85 (m, 1H), 4.19-4.37 (m, 2H), 5.19 (dd, *J* = 9.2, 15.1 Hz, 1H), 5.57 (dq, *J* = 6.4, 12.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 17.9, 22.4, 28.9, 31.7, 42, 80.4, 129.2, 129.3; mass spectrum *m/z* (relative intensity) EI 171 (0.2, M^+), 124 (12), 109 (7), 95 (7), 83 (19), 82 (100), 69 (29), 67 (43), 57 (13), 55 (80), 53 (10); HRMS (ESI) calculated for $[C_9H_{17}NNaO_2]^+$: 194.1151, found 194.1159.

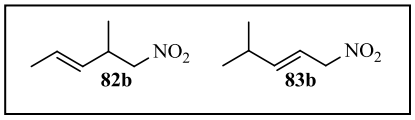
***(E)* 4-Methyl-1-nitroocta-2-ene (83a).** Employing general procedure C and using nitrodiene



83a

(113 mg, 1.0 mmol), LiCl (85 mg, 2.0 mmol), CuCN (1.0) and ^{n}BuLi (0.80 mL in hexane, 2.0 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave pure **83a** (130 mg, 76%) as colorelss oil: IR (neat) 2960 (s), 2930 (s), 2860 (s), 1556 (s), 1459 (s), 1376 (s), 1097 (s), 972 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.22-1.35 (m, 6H), 2.19-2.27 (m, 1H), 4.89 (d, *J* = 6.9 Hz, 2H), 5.67-6.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.8, 22.7, 29.3, 36.0, 36.6, 77.3, 116.8, 147.4; mass spectrum *m/z* (relative intensity) EI 171 (0.01, M^+), 124 (8), 109 (5), 95 (5), 83 (14), 82 (100), 69 (23), 67 (35), 55 (68); HRMS (ESI) calculated for $[C_9H_{17}NNaO_2]^+$: 194.1151, found 194.1156.

***(E)* 2-Methyl-nitropent-3-ene (82b) and *(E)* 4-Methyl-nitropent-2-ene (83b).** Employing

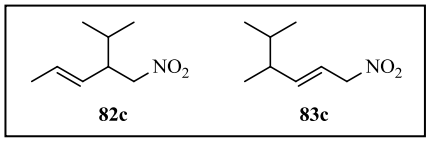


82b **83b**

general procedure B and using nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and MeMgCl (1.2 mL, 1.0 M in hexane, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82b** and **83b** (97 mg, 75%, regio 91:9) as colorless oil: IR (neat) 2963 (s), 2933 (s), 2859 (s), 1553 (s), 1469 (s), 1371 (s), 1087 (s), 974 cm^{-1}; **Major (82b):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, *J* = 6.9 Hz, 3H), 1.68 (d, *J* = 6.4 Hz, 3H), 2.95-3.04 (m, 1H), 4.23-4.30 (m, 2H), 5.31 (dd, *J* = 7.8, 15.6 Hz, 1H), 5.60 (dq, *J* = 6.4, 12.9 Hz, 1H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 17.6, 17.9, 36.2, 81.3, 127.7, 130.4; mass spectrum *m/z* (relative intensity) EI 129 (M^+, 0.14), 83 (21), 82 (99), 68 (12), 67 (97), 65 (9), 55 (100), 53 (28). **Minor (83b):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 6.5 Hz, 6H), 2.35-2.45 (m, 1H), 4.89 (d, J = 6.9 Hz, 2H), 5.71 (dt, J = 7.3, 16.9 Hz, 1H), 5.89 (dd, J = 6.4, 15.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 30.9, 77.6, 116.0, 148.2; mass spectrum *m/z* (relative intensity) EI 129 (M^+, 0.01), 83 (43), 67 (17), 55 (100), 53 (10).

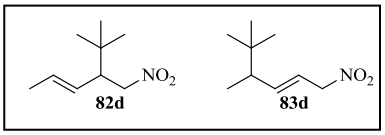
***(E)* 2-(1-Methylethyl)-1-nitropent-3-ene (82c)** and ***(E)* 4,5-Dimethyl-1-nitrohex-2-ene (83c).**



82c **83c**

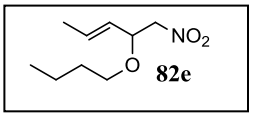
Employing general procedure A and using nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ^{i}PrMgBr (0.48 mL in Et_2O, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82c** and **83c** (119 mg, 76%, regio 88:12) as colorless oil: IR (neat) 2965 (s), 2868 (s), 1555 (s), 1436 (s), 1380 (s), 970 (s) cm^{-1}; **Major (82c):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 7.8 Hz, 6H), 1.70 (d, J = 6.0 Hz, 3H), 2.67 (sept, J = 5.5 Hz, 1H), 4.28 (t, J = 10.1 Hz, 1H), 4.45 (dd, J = 5.5, 11.0 Hz, 1H), 5.25 (dd, J = 9.2, 15.1 Hz, 1H), 5.55 (dq, J = 6.5, 12.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 18.8, 20.4, 29.8, 48.3, 79.0, 126.8, 130.2; mass spectrum *m/z* (relative intensity) EI 157 (0.05, M^+), 111 (10), 110 (92), 96 (14), 95 (90), 81 (29), 69 (84), 68 (99), 67 (95), 65 (9), 55 (99), 43 (100). **Minor (83c):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87-0.94 (m, 9H), 3.09-3.17 (m, 1H), 4.90 (d, J = 6.9 Hz, 2H), 4.70-5.74 (m, 1H), 5.88 (dd, J = 8.6, 15.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 19.7, 30.2, 42.2, 77.7, 117.7, 145.9; mass spectrum *m/z* (relative intensity) EI 157 (0.01, M^+), 134 (2), 111 (17), 110 (2), 99 (13), 95 (8), 81(14), 69 (95), 68 (100), 57 (23), 55 (78), 53 (16), 43 (74), 41 (71); HRMS (EI) calculated for $[C_8H_{14}NO_2]^+$: 156.10245, found 156.10227.

***(E)* 2-(2,2-Dimethylethyl)-1-nitropent-3-ene (82d)** and ***(E)* 4,5,5-Trimethyl-1-nitrohex-2-ene**



(83d). Employing general procedure B and using nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (225 mg, 1.0 mmol) and ^{t}BuLi (1.20 mL, 3.0 M in hexane, 3.0 mmol) in THF after purification by flash column chromatography (silica, 20-30% CH_2Cl_2:petroleum ether, v/v) gave **82d** and **83d** (123 mg, 72%, regio 56:44) as a colorless oil: IR (neat) 2965 (s), 2873 (s), 1656 (s), 1475 (s), 1376 (s), 972 (s) cm^{-1}; **Major (82d):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.67 (dd, J = 0.9, 6.4 Hz, 3H), 2.56-2.60 (m, 1H), 4.24 (t, J = 11.3 Hz, 1H), 4.52 (dd, J = 3.7, 11.0 Hz, 1H), 5.29-5.34 (m, 1H), 5.53 (dq, J = 6.4, 15.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 27.6, 32.6, 52.6, 77.9, 126.5, 130.6; mass spectrum *m/z* (relative intensity) EI 171 (0.3, M^+), 109 (15), 68 (63), 67 (18), 57 (100), 55 (13). HRMS (EI) calculated for $[C_9H_{17}NO_2]^+$: 171.1259, found 171.1253. **Minor (83d):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 9H), 0.97 (d, J = 6.9 Hz, 3H), 1.98-2.06 (m, 1H), 4.89 (d, J = 7.3 Hz, 2H), 5.67-5.73 (m, 1H), 5.89 (dd, J = 8.7, 15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 27.3, 32.9, 47.0, 77.7, 118.2, 145.0; mass spectrum *m/z* (relative intensity) EI 171 (0.01, M^+), 109 (14), 95 (14), 68 (59), 57 (100), 55 (12).

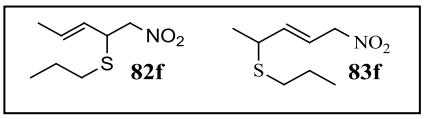
(*E*) 2-Butoxy-1-nitropent-3-ene (82e): Employing general procedure A and using sodium



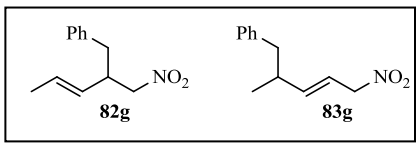
butoxide (3.0 mmol; prepared in situ during the reaction of ^{n}BuOH (222 mg) with NaH (72 mg) at 0 ^{o}C in THF for 30 min under argon), $ZnBr_2$ (225 mg, 1.0 mmol), nitrodiene (113 mg, 1.0 mmol) after purification by column chromatography (silica, 20-30% CH_2Cl_2:petroleum ether, v/v) gave **82e** (138 mg, 74%) as a colorless oil: IR (neat) 2967 (s), 2911 (s), 1557 (s), 1511 (s), 1247 (s), 1033 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H); 1.35 (sept, J = 7.8 Hz, 2H), 1.51 (pent, J = 6.4 Hz, 2H), 1.76 (d, J = 6.5 Hz, 3H), 3.26-3.33 (m, 1H), 3.51-3.56 (m, 1H), 4.28-4.48 (m, 3H), 5.31 (dd, J = 7.8, 15.2 Hz, 1H), 5.84-5.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 17.8, 19.2, 31.5, 68.7, 77.1, 79.1, 126.2,

132.2; mass spectrum *m/z* (relative intensity) EI 187 (M^+, 0.1), 143 (5), 127 (45), 125 (68), 114 (20), 111 (12), 85 (100), 71 (23); HRMS (EI) calculated for $[C_9H_{16}NO_3]^+$: 186.1130, found 186.1131.

***(E)* 2(1-Thiopropyl)-1-nitropent-3-ene (82f) and *(E)* 4-(1-Thiopropyl)-1-nitropent-2-ene (83f):** Employing general procedure B and using sodium thiobutoxide (3.0 mmol; prepared in situ by the reaction of ^{n}PrSH (228 mg) with NaH (72 mg) at 0 ^{o}C in THF for 30 min under argon), $ZnBr_2$ (225 mg, 1.0 mmol), nitrodiene (113 mg, 1.0 mmol) after purification by column chromatography (silica, 20-30% CH_2Cl_2:petroleum ether, v/v) gave **82f** and **83f** (149 mg, 79%, **82f:83f**, 20:80) as a colorless oil: IR (neat) IR (neat) 2938 (s), 2841 (s), 1633 (s), 1523 (s), 1367 (s), 915 (s), 767 (s) cm^{-1}; **Minor 82f:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, J = 7.6 Hz, 3H), 1.36 (d, J = 7.1 Hz, 3H), 1.56-1.64 (m, 2H), 2.39-2.47 (m, 2H), 3.40 (dt, J = 7.6, 14.6 Hz, 1H), 4.94 (d, J = 6.5 Hz, 2H), 5.71-5.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ13.5, 20.0, 22.9, 32.8, 41.1, 76.8, 117.7, 143.0; **Major 83f:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, J = 7.6 Hz, 3H), 1.60-1.65 (m, 2H), 1.73 (d, J = 5.5 Hz, 3H), 2.50-2.55 (m, 2H), 3.88-3.93 (m, 1H), 4.44-4.55 (m, 2H), 5.33-5.38 (m, 1H), 5.69 (dd, J = 6.5, 15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 17.7, 22.8, 30.0, 32.9, 44.6, 79.6, 126.9, 130.3. HRMS (EI) calculated for $[C_8H_{15}NO_2S]^+$: 189.0823, found 189.0824.

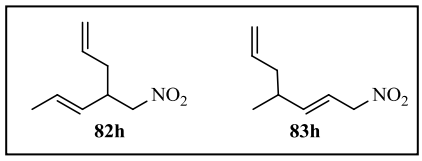


***(E)* 2-(Benzyl)-1-nitropent-3-ene (82g)** and ***(E)* 4-Methyl-5-phenyl-pent-2-ene (83g).** Employing method A, General procedure B and using benzyl bromide (342 mg, 2.00 mmol), magnesium (192 mg, 8 mmol), iodine (10 mg), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in Et_2O after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82g** and **83g** (182 mg, 89%. regio 82:18) as a colorless



oil. **Major (82g)**: IR (neat) 2927 (s), 2843 (s), 2811 (s), 1617 (s), 1527 (s), 1371 (s), 815 (s), 778 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.65 (dd, J = 0.9, 6.4 Hz, 3H), 2.66-2.82 (m, 2H), 3.12-3.19 (m, 1H), 4.20-4.34 (m, 2H), 5.30-5.34 (m, 1H), 5.55 (dq, J = 6.4, 12.9 Hz, 1H), 7.17-7.341 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 38.7, 43.3, 79.2, 126.7, 128.5, 128.6, 129.1, 129.3, 137.9; mass spectrum *m/z* (relative intensity) EI 205 (0. 06, M^+), 157 (7), 144 (20), 129 (25), 128 (10), 117 (12), 115 (12), 105 (10), 92 (46), 91 (100), 77 (7), 68 (84), 32 (32), 55 (11), 51 (7); Anal.Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82 %; found C, 70.58; H, 7.58; N, 6.89 %. **Minor (83g)**: IR (neat) 2933 (s), 2866 (s), 2819 (s), 1543 (s), 1353 (s), 817 (s), 769 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, J = 6.4 Hz, 3H), 2.54-2.72 (m, 3H), 4.86 (d, J = 7.4 Hz, 2H), 5.67 (dt, J = 7.4, 14.6 Hz, 1H), 5.88 (dd, J = 6.9, 15.5 Hz, 1H), 7.13-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 38.2, 42.8, 77.6, 117.3, 126.1, 128.2, 129.1, 139.7, 146.0; mass spectrum *m/z* (relative intensity) EI 205 (0. 14, M^+), 159 (3), 144 (6), 128 (3), 105 (4), 92 (12), 91 (100), 77 (3), 68 (46), 65 (14), 55 (4), 51 (3). Anal.Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82 %; found C, 70.58; H, 7.58; N, 6.89 %.

(E) **2-(2-Propenyl)-1-nitropent-3-ene (82h)** and ***(E)*** **4-Methyl-2,6-heptadiene (83h).**

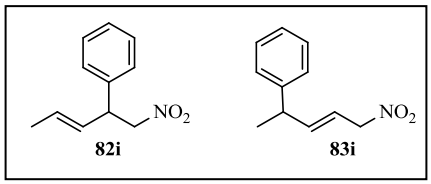


82h 83h

Employing general procedure B and using nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (12 mg, 0.1 mmol) and allyl magnesium bromide (1.2 mL, 1.0 M in THF, 1.2 mmol) in THF after purification by flash column chromatography (silica, 15-20% CH_2Cl_2:petroleum ether, v/v) gave the mixture of **82h** and **83h** (regio, 96:4, 132 mg, 85%) as a colorless oil. IR (neat) 2963 (s), 2843(s), 2807 (s), 1613 (s), 1534 (s), 1531 (s), 1356 (s) cm^{-1}; **Major (82h):** ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (d, J = 6.4 Hz, 3H), 2.12-2.24 (m, 2H), 2.93 (dt, J = 7.4, 15.2 Hz, 1H), 4.23 (dd, J = 8.7, 11.5 Hz, 1H), 4.40 (d, J = 6.0 Hz, 11.9 Hz, 1H), 5.01-5.11 (m, 2H), 5.27 (dd, J = 8.7, 15.6 Hz, 1H), 5.55-5.62 (m, 1H), 5.70-5.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9,

36.6, 41.2, 79.4, 117.9, 128.7, 129.1, 134.3; mass spectrum *m/z* (relative intensity) EI 155 (0.01, M^+), 93 (34), 79 (38), 68 (100), 67 (98), 55 (60); HRMS (EI) calculated for $[C_8H_{13}NO_2]^+$: 155.0946, found 155.0948; **Minor (83h):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 6.9 Hz, 3H), 2.05-2.11 (m, 1H), 2.29-2.37 (m, 1H), 3.33-3.42 (m, 1H), 4.89 (d, J = 6.9 Hz, 2H), 5.01-5.21 (m, 3H), 5.65-5.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 36.6, 40.5, 77.6, 117.2, 127.9, 128.5, 134.2; mass spectrum *m/z* (relative intensity) EI 155 (0.01, M^+), 93 (26), 79 (37), 68 (100), 67 (97), 55 (62).

***(E)* 2-Phenyl-1-nitropent-3-ene (82i)** and ***(E)* 4-Phenyl-pent-2-ene (83i)**. Employing general procedure B and using nitrodiene (113 mg, 1.0 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) and PhMgCl

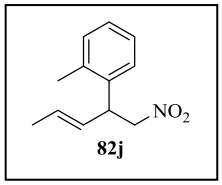


82i 83i

(0.48 mL, 2.5 M in Et_2O, 1.2 mmol) in CH_2Cl_2 after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82i** and **83i** (162 mg, 85%, regio, 98:2) as colorless oil. IR (neat) 2929 (s), 2856 (s), 2809 (s), 1609 (s), 1531 (s), 1527 (s), 1363 (s), 753 (s) cm^{-1}; **Major (82i):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (d, J = 5.1 Hz, 3H), 4.06 (q, J = 7.4 Hz, 1H), 4.52 (d, J = 8.2 Hz, 2H), 5.49-5.57 (m, 2H), 7.13-7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 47.2, 80.0, 127.4, 127.6, 128.5, 129.0, 129.1, 138.9; mass spectrum *m/z* (relative intensity) EI 191 (0.14, M^+), 145 (18), 144 (91), 143 (16), 131 (22), 129 (100), 128 (33), 117 (22), 115 (37), 103 (19), 81 (62), 77 (22), 65 (14), 51 (15). Anal.Calcd for $C_{11}H_{13}NO_2$; C, 69.09; H, 6.85; N, 7.32 %; found C, 69.07; H, 6.96; N, 7.30 %; **Minor (83i):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, J = 7.4 Hz, 3H), 3.58 (dq, J = 6.9, 13.7 Hz, 1H), 4.92 (d, J = 7.4 Hz, 2H), 5.81 (dt, J = 6.9, 14.7 Hz, 1H), 6.10 (dd, J = 6.4, 15.1 Hz, 1H), 7.20-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 42.0, 77.3, 117.5, 126.6, 127.2, 128.6, 129.0, 145.5; mass spectrum *m/z* (relative intensity) EI 191 (0.61, M^+), 145 (100), 130 (28), 128 (25), 117 (47), 115

(42), 105 (27), 91 (62), 77 (23), 65 (14), 51 (18) Anal.Calcd for $C_{11}H_{13}NO_2$; C, 69.09; H, 6.85; N, 7.32 %; found C, 69.07; H, 6.96; N, 7.30 %.

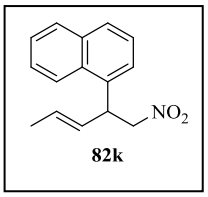
(*E*) 2-(2-Methylphenyl)-1-nitropent-3-ene (82j) 2-(2-Methylphenyl)-1-nitropent-3-ene (83j). Employing method A, general procedure B and using 2-bromotoulene (206 mg, 1.2 mmol), magnesium (192 mg, 8.0 mmol), iodine (10 mg), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave



82j

82j (178 mg, 87%: regio 92:8) as a colorless oil. IR (neat) 3057 (s), 2911 (s), 1594 (s), 1556 (s), 1431 (s), 1373 (s), 974 (s), 787 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, J = 5.5 Hz, 3H), 2.41 (s, 3H), 4.44 (q, J = 7.8 Hz, 1H), 4.60-4.66 (m, 2H), 5.54-5.62 (m, 2H), 7.16-7.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 19.4, 42.7, 79.2, 125.9, 126.5, 127.3, 128.3, 129.0, 131.0, 136.0, 137.0; mass spectrum *m/z* (relative intensity) EI 205 (16.37, M^++1), 241 (89, M^+), 195 (29), 194 (74), 181 (67), 179 (98), 166 (87), 165 (100), 153 (66), 152 (64), 141 (25), 115 (25), 89 (19), 76 (13), 67 (14); HRMS (EI) calculated for $[C_{15}H_{15}NO_2]^+$: 205.1103, found 205.1105.

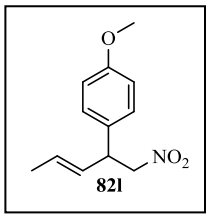
(*E*) 2-(1-Napthanyl)-1-nitropent-3-ene (82k). Employing method A, general procedure B and using 1-bromonapthalene (414 mg, 2.00 mmol), magnesium (192 mg, 8.0 mmol), iodine (10 mg), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82k** (200 mg, 83%, regio 100:0) as a colorless oil. IR (neat) 3050 (s), 2917 (s), 1598 (s), 1553 (s), 1433 (s), 1378 (s), 969 (s), 779 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (d, J = 5.0 Hz, 3H), 4.72-4.80 (m, 2H), 5.03-5.07 (m, 1H), 5.71-5.81 (m, 2H), 7.38-8.20 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 42.1, 79.4, 122.5, 124.2, 125.4, 125.9, 126.7, 128.2, 128.3, 129.2, 129.6, 130.9, 134.1, 134.8; mass spectrum *m/z* (relative



82k

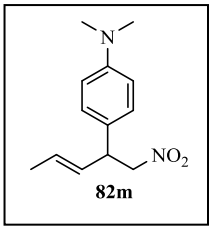
intensity) EI 242 (16.37, M^++1), 241 (89, M^+), 195 (29), 194 (74), 181 (67), 179 (98), 166 (87), 165 (100), 153 (66), 152 (64), 141 (25), 115 (25), 89 (19), 76 (13), 67 (14); HRMS (EI) calculated for $[C_{15}H_{15}NO_2]^+$: 241.1103, found 241.1102.

(*E*) 2-(4-Methoxyphenyl)-1-nitropent-3-ene (82l). Employing method A, general procedure B and using 4-bromoanisole (374 mg, 2.00 mmol), magnesium (192 mg, 8.0 mmol), iodine (10 mg), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82l** (161 mg, 73%, regio 100:0) as colorless oil. IR (neat) 2963 (s), 2919 (s), 2833 (s), 1553 (s), 1514 (s), 1252 (s), 1033 (s), 832 (s), 750 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, J = 4.6 Hz, 3H), 3.80 (s, 3H), 4.07-4.13 (m, 1H), 4.54-4.63 (m, 2H), 5.57-5.63 (m, 2H), 6.89 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 46.4, 55.3, 80.2, 114.4, 128.4, 128.7, 128.8, 130.9, 158.9; mass spectrum *m/z* (relative intensity) EI 221 (13.32, M^+), 175 (22), 174 (100), 161 (60), 160 (23), 159 (93), 146 (20), 144 (23), 143 (24), 128 (28), 121 (35), 115 (32), 107 (14), 91 (64), 77 (29), 65 (25), 55 (18), 51 (14); HRMS (ESI) calculated for $[C_{12}H_{15}NO_3]^+$: 221.1052, found: 221.1050.



82l

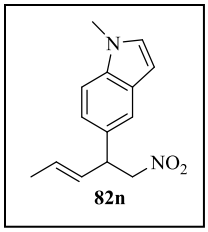
(*E*) 2-(4-*N*,*N*-Dimethylaminophenyl)-1-nitropent-3-ene (82m). Employing method A, general procedure B and using *N*,*N*-dimethyl-4-bromoaniline (400 mg, 2.00 mmol), magnesium (192 mg, 8.0 mmol), iodine (10 mg), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82m** (168 mg, 72%, regio 100:0) as colorless oil: IR (neat) 2923 (s), 2853 (s), 2800 (s), 1614 (s), 1551 (s), 1522 (s), 1378 (s), 815 (s), 750 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71 (d, J = 4.1 Hz, 3H)



82m

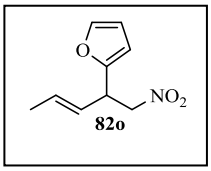
2.96 (s, 6H), 4.08 (dt, *J* = 5.1, 12.4 Hz, 1H), 4.58 (d, *J* = 7.4 Hz, 2H), 5.62 (d, *J* = 4.1 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 40.7, 46.6, 80.5, 113.0, 128.1, 128.2, 128.3, 129.3, 149.9; mass spectrum *m/z* (relative intensity) EI 234 (42.70, M^+), 188 (16), 187 (35), 174 (100), 172 (28), 159 (35), 158 (23), 146 (17), 144 (23), 132 (14), 128 (14), 115 (12), 91 (10), 77 (11), 65 (5). Anal.Calcd calculated for $C_{13}H_{18}N_2O_2$; C, 66.64; H, 7.74; N, 11.96%; found C, 66.95; H, 7.85; N, 11.86%.

(*E*) 2-(5-(1-Methylindolyl))-1-nitropent-3-ene (82n). Employing method C, general procedure B, and using 5- iodo-(1-methyl)-indole (386 mg, 1.5 mmol), ^{i}PrMgCl (0.78 mL, 2.0 M in Et_2O, 1.5 mmol), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82n** (207 mg, 73%, regio 100:0) as colorless oil: IR (neat) 2913 (s), 2918 (s), 1550 (s), 1475 (s), 1423 (s), 1377 (s), 967 (s), 791 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (d, *J* = 5.1 Hz, 3H), 3.71 (s, 3H), 4.38 (q, *J* = 7.3 Hz, 1H), 4.57-4.69 (m, 2H), 5.60-5.70 (m, 2H), 6.84-7.93 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 32.9, 39.0, 79.5, 82.9, 111.4, 111.6, 126.9, 127.7, 128.0, 128.8, 129.0, 130.5, 136.3; mass spectrum *m/z* (relative intensity) EI 244 (44, M^+), 197 (32), 184 (100), 182 (45), 167 (27), 168 (32), 157 (9), 146 (9), 128 (10), 115 (14), 91 (7), 77 (9); HRMS (ESI) calculated for $[C_{14}H_{16}N_2NaO_2]^+$: 267.1104, found 267.1119.



82n

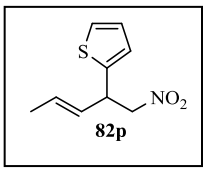
(*E*) 2-(2-Furyl)-1-nitropent-3-ene (82o). Employing method B, general procedure B, and using furan (136 mg, 2.00 mmol), TMEDA (232 mg, 2.0 mmol), ^{n}BuLi (2.0 mmol, 0.8 mL, 2.5 M in hexane), magnesium (51 mg, 2.2 mmol), iodine (10 mg), 1,2-dibromoethane (0.17 mL, 2.0 mmol), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in Et_2O after purification by flash column chromatography (silica, 10-



82o

20%, CH_2Cl_2:petroleum ether, v/v) gave **82o** (150 mg, 83%, regio 100:0) as a colorless oil: IR (neat) 2921 (s), 2852 (s), 1555 (s), 1507 (s), 1378 (s), 1012 (s), 968 (s), 740 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (dd, J = 1.0, 6.4 Hz, 3H), 4.26 (q, J = 8.3 Hz, 1H), 4.52-4.56 (m, 1H), 4.71-4.74 (m, 1H), 5.51-5.57 (m, 1H), 5.68-5.73 (m, 1H), 6.14 (d, J = 3.0 Hz, 1H), 6.32-6.34 (m, 1H), 7.37 (t, J = 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 41.2, 77.9, 106.7, 110.4, 125.5, 130.8, 142.3, 151.9; mass spectrum *m/z* (relative intensity) EI 181 (0.72, M^+), 135 (11), 134 (100), 133 (12), 119 (23), 106 (5), 105 (29), 93 (12), 91 (66), 79 (13), 77 (25), 65 (16), 55 (18), 53 (10). Anal.Calcd calculated for $C_{12}H_{15}NO_2$: C, 59.66; H, 6.12; N, 7.73 %; found C, 59.39; H, 6.33; N, 7.92 %.

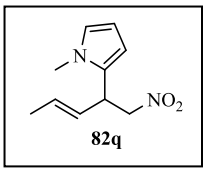
(*E*) 2-(2-Thienyl)-1-nitropent-3-ene (82p). Employing method B, general procedure B and using



82p

thiophene (168 mg, 2.00 mmol), TMEDA (232 mg, 2.0 mmol), ^{n}BuLi (0.8 mL, 2.5 M in hexane, 2.0 mmol), magnesium (51 mg, 2.2 mmol), iodine (10 mg) 1,2-dibromoethane (0.17 mL, 2.0 mmol), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in Et_2O after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82p** (160 mg, 81%, regio 100:0) as a colorless oil: IR (neat) 3031 (s), 2920 (s), 2861 (s), 1555 (s), 1433 (s), 1378 (s), 966 (s), 703 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (d, J = 6.4 Hz, 3H), 4.45 (q, J = 7.8 Hz, 1H), 4.55-4.71 (m, 2H), 5.59 (dd, J = 8.3, 15.5 Hz, 1H), 5.69-5.75 (m, 1H), 6.90 (d, J = 3.7 Hz, 1H), 6.98 (t, J = 4.1 Hz, 1H), 7.25 (d, J = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 42.5, 80.2, 124.6, 124.7, 127.1, 128.0, 129.9, 141.9; mass spectrum *m/z* (relative intensity) EI 197 (M^+, 2.05), 152 (11), 151 (28), 150 (99), 149 (48), 137 (52), 135 (100), 123 (10), 117 (18), 115 (15), 109 (15), 105 (13), 97 (57), 91 (40), 77 (20), 67 (25), 65 (25), 59 (19); HRMS (ESI) calculated for $[C_9H_{11}NNaO_2S]^+$: 220.0403, found 220.0392.

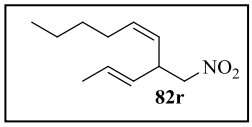
(*E*) 2-(2-(1-Methylpyrrolyl))-1-nitropent-3-ene (82q). Employing method B, general procedure



82q

B and using 1-methylpyrrol (162 mg, 2.00 mmol), TMEDA (232 mg, 2.0 mmol), ^{n}BuLi (2.0 mmol, 0.8 mL, 2.5 M in hexane), magnesium (51 mg, 2.2 mmol), iodine (10 mg), 1,2-dibromoethane (0.17 mL, 2.0 mmol), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in Et_2O after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82q** (153 mg, 79%, regio 100:0) as a colorless oil. IR (neat) 3023 (s), 2920 (s), 1555(s), 1491 (s), 1379 (s), 1301(s), 1092 (s), 969 (s), 713 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (d, J = 6.4 Hz, 3H), 3.59 (s, 3H), 4.21 (q, J = 7.3 Hz, 1H), 4.56-4.68 (m, 2H), 5.43 (ddd, J = 1.4, 7.8, 15.1, 1H), 5.57-5.66 (m, 1H), 5.93 (d, J = 3.2 Hz, 1H), 6.09 (d, J = 2.3 Hz, 1H), 6.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 33.7, 39.1, 78.6, 105.2, 107.0, 122.6, 127.9, 129.3, 129.5; mass spectrum *m/z* (relative intensity) EI 195 (9, M^++1), 194 (65, M^+),148 (14), 146 (39), 146 (16), 134 (100), 132 (95), 119 (15), 118 (20), 117 (28), 110 (13), 107 (22), 106 (15), 96 (47), 93 (31), 91 (23), 79 (14), 77 (16), 67 (21), 65 (14), 53 (9), 51 (7); HR-EI calculated for $[C_{10}H_{15}N_2O_2]^+$: 195.1128, found 195.1144.

(E) **2-(1-Propenyl)-1-nitrooct-3-ene (82r).** Employing method C, general procedure B and using

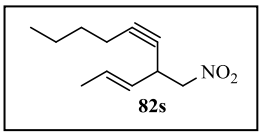


82r

nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), 1-iodo-1-hexene (252 mg, 1.2 mmol), ^{n}BuLi (0.48 mL, 2.5M in hexane) in Et_2O after purification by flash column chromatography (silica, 15-20%, CH_2Cl_2:petroleum ether, v/v) gave **82r** (168 mg, 85%, regio, 100:0) as a colorless oil: IR (neat) 2966 (s), 2843 (s), 2817 (s), 1619 (s), 1533 (s), 1523 (s), 1352 (s) cm^{-1}; 0.90 (t, J = 7.4 Hz, 3H), 1.27-1.36 (m, 4H), 1.69 (d, J = 6.9 Hz, 3H), 2.01-2.05 (m, 2H), 3.48-3.53 (m, 1H), 4.33 (d, J = 5.2 Hz, 2H), 5.26-5.38 (m, 2H), 5.53-5.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 18.0, 22.1, 31.3, 32.2, 44.7, 79.8, 126.7, 128.1, 128.6, 134.2; mass spectrum *m/z* (relative intensity) EI 197 (0.01, M^+), 150 (13),

107 (26), 93 (100), 79 (36), 67 (26); HRMS (EI) calculated for $[C_{11}H_{19}NO_2]^+$: 197.1416, found 197.1420.

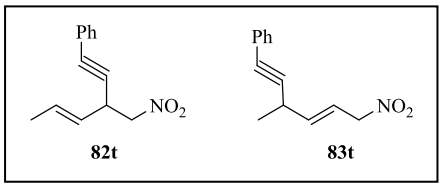
(*E*) 2-(1-Propene)-1-nitrooct-3-yne (82s). Employing method B, general procedure B and using



82s

1-hexyne (164 mg, 2.00 mmol), ^{n}BuLi (2.0 mmol, 0.8 mL, 2.5 M in hexane), magnesium (51 mg, 2.2 mmol), iodine (10 mg), 1,2-dibromoethane (0.17 mL, 2.0 mmol), nitrodiene (113 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) in Et_2O after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **82s** (148 mg, 76%, regio 100:0) as a colorless oil: IR (neat) 2958 (s), 2934 (s), 2868 (s), 1557 (s), 1377 (s), 965 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.36-1.51 (m, 4H), 1.72 (d, J = 6.9 Hz, 3H), 2.17-2.21 (m, 1H), 3.85 (q, J = 8.7 Hz, 1H), 4.32-4.44 (m, 2H), 5.35 (dd, J = 1.9, 6.9 Hz, 1H), 5.86 (dq, J = 6.4, 13.7 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 17.7, 18.3, 21.8, 30.7, 33.9, 75.4, 79.1, 86.1, 125.3, 130.1; mass spectrum *m/z* (relative intensity) EI 195 (0.02, M^+), 149 (27), 148 (99), 133 (30), 119 (54), 107 (24), 106 (62), 105 (87), 103 (14), 93 (47), 91 (100), 81 (20), 79 (75), 67 (39), 55 (60), 53 (20). Anal.Calcd calculated for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17 %; found C, 67.41; H, 8.53; N, 7.02 %.

(*Z*) 2-(2-Phenylacetylene)-1-nitropent-3-ene (82t) and (*Z)* 4-(2-Phenylacetylene)-1-nitropent-2-ene (83t). Employing method B, general procedure B and using 1-phenylacetylene (204 mg,

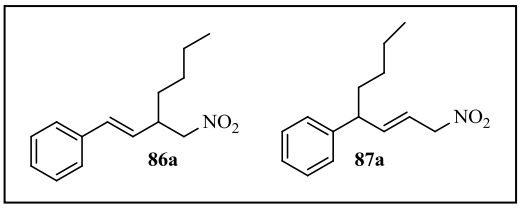


82t **83t**

2.00 mmol), ^{n}BuLi (2.0 mmol, 0.8 mL, 2.5 M in hexane], magnesium (51 mg, 2.2 mmol), iodine (10 mg), 1,2-dibromoethane (0.17 mL, 2.0 mmol) nitrodiene (113 mg, 1.0 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) in Et_2O after purification by flash column chromatography (silica, 20% CH_2Cl_2:petroleum ether, v/v) gave **82t** and **83t** (178 mg, 83%, regio 93:7) as a colorless oil: IR (neat) 2978 (s), 2929 (s), 2868 (s), 1555 (s), 1590 (s), 1375 (s), 969 (s),

758 (s), 692 (s) cm^{-1}; **Major (82t)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (d, J = 6.4 Hz, 3H), 4.11 (q, J = 6.9 Hz, 1H), 4.45-4.58 (m, 2H), 5.46 (dd, J = 6.9, 15.1 Hz, 1H), 6.97 (dq, J = 6.4, 13.3 Hz, 1H), 7.32-7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 34.3, 78.6, 84.7, 85.5, 122.4, 124.5, 128.3, 128.4, 130.8, 131.7; mass spectrum *m/z* (relative intensity) EI 216 (6.4, M^+ +1), 215 (43, M^+), 169 (95), 167 (28), 165 (19), 154 (100), 153 (91), 142 (14), 141 (81), 129 (42), 128 (70), 115 (51), 102 (15), 91 (67), 77 (39), 76 (21), 65 (18), 51 (21); HR-EI calculated for $[C_{13}H_{14}NO_2]^+$: 216.1019, found 216.1021. **Minor (83t)**: IR (neat) 3027 (s), 2921 (s), 2851 (s), 1556 (s), 1490 (s), 1377 (s), 965 (s), 758 (s), 692 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, J = 6.9 Hz, 3H), 3.43-3.52 (m, 1H), 4.97 (d, J = 7.3 Hz, 2H), 5.97 (dd, J = 5.5, 15.1 Hz, 1H), 6.09-6.17 (m, 1H), 7.32-7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 29.1, 77.2, 83.3, 89.9, 118.6, 123.2, 128.0, 128.2, 131.6, 141.2; mass spectrum *m/z* (relative intensity) EI 215 (2, M^+), 168 (81), 167 (100), 165 (25), 154 (27), 153 (85), 152 (55), 142 (26), 141 (25), 129 (59), 128 (54), 115 (16), 105 (33), 102 (23), 91 (41), 89 (32), 77 (58), 65 (17), 51 (20); HR-EI calculated for $[C_{13}H_{14}NO_2]^+$: 216.1019, found 216.1016.

(E) **2-(2'-Phenylethylene)-1-nitrohexane (86a)** and ***(E)*** **4-Phenyl 1-nitrooct-2-ene** (**87a)**:

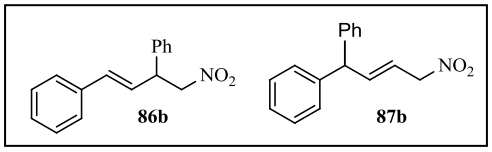


86a **87a**

Employing general procedure B and using nitrodiene **19I** (88 mg, 0.5 mmol), $ZnBr_2$ (12 mg, 0.05 mmol) and $^{n}BuMgCl$ (0.24 mL, 2.5 M in THF, 0.6 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2: petroleum ether, v/v) gave **86a** and **87a** (78 mg, 67%: regio 80:20) as colarless oil. IR (neat) 2939 (s), 2855 (s), 2813 (s), 1617 (s), 1534 (s), 1371 (s), 748 (s) cm^{-1}; **Major (86a):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, J = 5.1 Hz, 3H), 1.06-1.44 (m, 5H), 1.60 (q, J = 7.4 Hz, 1H), 2.91-2.97 (m, 1H), 4.26-4.37 (m, 2H), 5.87 (dd, J = 9.2, 16.0 Hz, 1H), 6.40 (d, J = 15.6 Hz, 1H), 7.19-7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.5,

29.0, 31.8, 42.3, 80.1, 126.4, 127.6, 128.6, 128.9, 133.3, 139.6; mass spectrum *m/z* (relative intensity) EI 233 (M^+, 5.0), 186 (24), 144 (65), 130 (33), 129 (100), 117 (31), 115 (33), 107 (20), 91 (80), 77 (9), 65 (5), 55 (22), 41 (19); **Minor 87a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (t, J = 7.4 Hz, 3H), 1.06-1.44 (m, 4H), 3.45 (dt, 6.4, 15.2 Hz, 1H), 4.40-4.49 (m, 2H), 4.79 (d, J = 6.9 Hz, 2H), 5.67 (dt, J = 7.6, 15.6 Hz, 1H), 5.95 (dd, J = 7.8, 15.6 Hz, 1H); 7.08-7.18 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 22.4, 29.1, 32.8, 44.3, 81.0, 127.5, 127.6, 127.8, 127.9, 128.7, 136.0; mass spectrum *m/z* (relative intensity) EI 233 (M^+, 0.5), 187 (21), 145 (9), 128 (34), 129 (44), 117 (68), 105 (14), 91 (100), 83 (7), 77 (7), 65 (5), 55 (9), 41 (16). HRMS (EI) calculated for $[C_{14}H_{19}NO_2]^+$: 233.1416, found 233.1418.

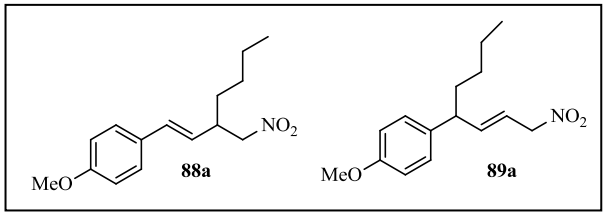
(*E*) 2,4-Diphenyl-1-nitrobut-3-ene (86b) and (*E*)-4,4-Diphenyl-1-nitrobut-2-ene (87b):



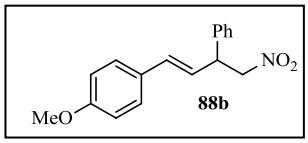
Employing general procedure B and using nitrodiene **19I** (175 mg, 1.0 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) and PhMgCl (0.48 mL 2.5 M in Et_2O, 1.2 mmol) in THF after purification by flash column chromatography (silica, 20-30% CH_2Cl_2:petroleum ether, v/v) gave **86b** and **87b** (195 mg, 77%, regio 65:35) as a white amorophous solid: IR (neat) 2932 (s), 2856 (s), 2815 (s), 1611 (s), 1537 (s), 1367 (s), 748 (s), 741 (s) cm^{-1}; **Major 86b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (q, J = 7.8 Hz, 1H), 4.62-4.70 (m, 2H), 6.23 (dd, J = 7.8, 16.0 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 7.15-7.30 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.0, 79.3, 126.6, 127.7 (2-carbons), 127.8,128.0, 128.7, 129.1, 129.3, 133.0, 139.3; mass spectrum *m/z* (relative intensity) EI 253 (M^+0.04), 193 (23), 180 (100), 165 (82), 152 (16), 139 (4), 115 (9), 103 (37), 77 (39), 51 (22). **Minor 87b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (d, J = 7.3 Hz, 1H), 4.90 (d, J = 8.3 Hz, 3H), 7.17-7.30 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.4, 79.8, 127.1, 127.5, 127.7 (2-carbons), 128.0, 128.4, 128.9, 129.4, 136.3, 138.5; mass spectrum *m/z* (relative intensity) EI 253

(M^+ 0.9), 219 (10), 206 (36), 191 (13), 178 (9), 165 (8), 141 (4), 127 (17), 128 (19), 115 (39), 103 (14), 91 (100), 77 (18), 65 (14), 51 (11).

(*E*) 2-Butyl-4-(4-methoxyphenyl)-1-nitrobut-3-ene (88a) and (*E*) 4-(4-Methoxy)-1-nitrooct-2-ene (89a): Employing general procedure B and using nitrodiene **19II** (104 mg, 0.5 mmol), $ZnBr_2$ (12 mg, 0.05 mmol) and ^{n}BuMgCl (0.24 mL, 2.5M in THF, 0.6 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **88a** and **89a** (96mg, 73%, regio 78:22) as a colorless oil: IR (neat) 2937 (s), 2851 (s), 2803 (s), 1622 (s), 1533 (s), 1367 (s), 756 (s) cm^{-1}. **Major 88a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H), 1.22-1.38 (m, 6H), 2.98-3.03 (m, 1H), 3.82 (s, 3H), 4.34-4.48 (m, 2H), 5.80 (dd, J = 9.2, 15.6 Hz, 1H), 6.44 (d, J = 16.1 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.4, 28.9, 31.8, 42.3, 55.3, 80.2, 113.9, 125.6, 127.5, 132.6, 145.2, 159.3; mass spectrum *m/z* (relative intensity) EI 264 (M^++1, 4.0), 263 (M^+, 22), 216 (11), 203 (6), 174 (37), 160 (32), 159 (76), 147 (36), 129 (22), 121 (100), 115 (32), 103 (6), 91 (39), 77 (19), 65 (8); HRMS (EI) calculated for $[C_{15}H_{21}NO_3]^+$: 263.1521, found 263.1520. **Minor 89a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.22-1.38 (m, 4H), 1.68-1.74 (m, 2H), 3.26-3.31 (m, 1H), 3.81 (s, 3H), 4.89 (d, J = 7.4 Hz, 2H), 5.75 (dd, J = 7.8, 14.7 Hz, 1H), 6.01 (dd, J = 7.8, 14.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.5, 29.6, 34.9, 47.6, 55.2, 77.3, 114.0, 117.6, 128.5, 129.3, 135.0, 158.2.

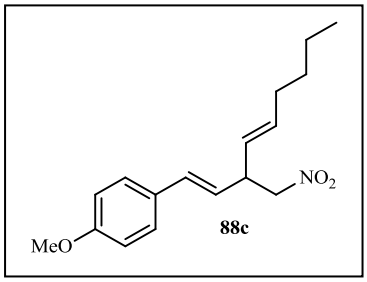


***(E)* 2-Phenyl-(4-methoxyphenyl)-1-nitrobut-3-ene (88b):** Employing general procedure B and using nitrodiene **19II** (104 mg, 0.5 mmol), $ZnBr_2$ (12 mg, 0.05 mmol) and PhMgCl (0.24 mL, 2.5



M in Et_2O, 0.6 mmol) in THF after purification by flash column chromatography (silica, 20-30% CH_2Cl_2:petroleum ether, v/v) gave **88b** (100 mg, 71%) as a pale yellow solid: IR (neat) 2927 (s), 2867 (s), 2811 (s), 1617 (s), 1530 (s), 1367 (s), 759 (s), 747 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 4.24-4.30 (m 1H), 4.63-4.67 (m, 2H), 6.09 (dd, J = 8.3, 16.1 Hz, 1H), 6.37 (d, J = 15.6 Hz, 1H), 6.75 (d, J = 8.8 Hz, 2H), 7.18-7.27 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.3, 55.3, 79.8, 113.9, 124.7, 127.5, 127.7, 127.9, 129.1, 132.3, 138.6, 146.8, 159.4; mass spectrum *m/z* (relative intensity) EI 284 (M^++1, 4.0), 283 (M^+, 21), 236 (74), 223 (23), 207 (42), 191 (12), 178 (16), 159 (18), 145 (41), 129 (24), 121 (80), 103 (23), 91 (100), 77 (33), 65 (14). HRMS (EI) calculated for $[C_{17}H_{17}NO_3]^+$: 283.1208, found 283.1210.

(*E*) 2-(2'-(4-Methoxyphenyl)-1-nitrooct-2-ene (88c): Employing method C, general procedure

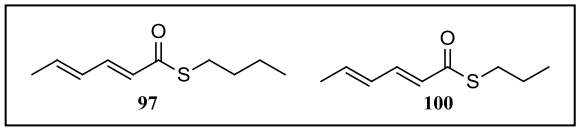


B and using nitrodiene **19II** (103 mg, 0.5 mmol), $ZnBr_2$ (12 mg, 0.05 mmol) 1-iodo-1-hexene (252 mg, 1.2 mmol), ^{n}BuLi (0.48 mL, 2.5M in hexane) in Et_2O after purification by flash column chromatography (silica, 15-20% CH_2Cl_2:petroleum ether, v/v) gave **88c** as pale yellow solid (98 mg, 68%, regio, 100:0) as colorless solid: IR (neat) 2963 (s), 2845 (s), 2827 (s), 1623 (s), 1543 (s), 1525 (s), 1357 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3H), 1.27-1.38 (m, 4H), 2.05 (q, J = 6.4 Hz, 2H), 3.68-3.74 (m, 1H), 3.82 (s, 3H), 4.44 (dd, J = 2.8, 7.8 Hz, 2H), 5.40 (dd, J = 7.8, 15.6 Hz, 1H), 5.65 (dt, J = 8.3, 15.6 Hz, 1H), 5.93 (dd, J = 7.8, 16.0 Hz, 1H), 6.44 (d, J = 16.1 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.1, 31.2, 32.2, 44.9, 55.3, 79.6, 113.9, 124.3, 126.3, 127.5, 129.2, 132.0, 134.8, 159.4; mass spectrum *m/z* (relative intensity) EI 289 (8.0, M^+), 242 (22), 228 (15), 211(5), 199 (10), 185 (36), 171 (18),

159 (17), 141 (18), 128 (13), 121(100), 115 (17), 91 (21), 77 (13), 67 (8), 55 (13). HRMS (ESI) calculated for $[C_{17}H_{23}NO_3Na)^+$: 312.1570, found 312.1551.

Synthesis of *α,β,γ,δ* Unsaturated Thioesters

α,β,γ,δ-Unsaturated thioester was prepared by using literature procedure.[75] To the solution of

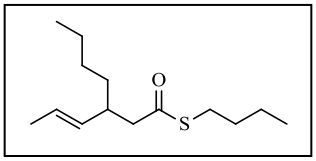


sorbic acid (1.12 g, 10.0 mmol) and ^{n}BuSH (1.08 g, 12.0 mmol) in CH_2Cl_2 (30 mL) was added dicyclohexylcarbodimide (DCC, 2.15 g, 10.5 mmol) and 4-dimethylaminopyridine (DMAP, 122 mg) at 0 ^oC and the resulting mixture was stirred with slowly warming up to room temperature over 12 hours. The mixture was filter through a short pad of celite and the precipitate was washed with CH_2Cl_2. The filtrate was washed subsequently with saturated aqueous $NaHCO_3$ (2 x 20.0 mL), water (20.0 mL) and brine (20.0 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. Distillation of crude product using Kugelrohr vacuum distillation gave pure product **97** as colorless oil (1.28 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0. 92 (t, J = 7.3 Hz, 3H), 1.38-1.43 (m, 2H), 1.57-1.61 (m, 2H), 1.86 (d, J = 5.9 Hz, 3H), 2.95 (t, J = 6.9 Hz, 2H), 6.05-6.23 (m, 3H), 7.15-7.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 18.9, 22.1, 28.5, 31.8, 126.3, 129.7, 140.7, 140.9, 190.3. The use of ^{n}PrSH (0.91 g, 12.0 mmol) under identical conditions gave thiodiaonate **100** (2.96 g, 87%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.59 (sext, 7.4 Hz, 2H), 1.81 (d, J = 6.0 Hz, 3H), 2.88 (t, J = 7.4 Hz, 2H), 6.02-6.17 (m, 3H), 7.13 (dd, J = 15.1, 10.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 18.8, 23.0, 30.5, 126.2, 129.6, 140.6, 140.7, 190.1.

General Procedure E: Zinc (II) Salts Catalyzed Reaction of Grignard Reagents with Thiodionate (97 and 100), Ketodiene (103) and Sorbate Ester (107). To the flame dried ZnX_2 (0.1 mmol) in THF or Et_2O or CH_2Cl_2 or toluene (4.0 mL) under argon was added *α,β,γ,δ*

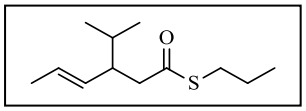
unsaturated thioester **97** or **100** (1.0 mmol) or ketodiene (**103**) or sorbate ester (**107**) and the resulting solution was cooled to -20 ^{o}C. Grignard reagent (1.2 mmol) was added and the mixture was stirred for 2-12 hours with gradual warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (5.0 mL), filtered and the filtrate was extracted with Et_2O (3 x 10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography silica (10-20% CH_2Cl_2:petroleum ether, v/v).

(*E*) *n*-Butyl 3-(1-propenyl)-hexenylthieonate (98a). Employing general procedure E and using



thioester **97** (184 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **98a** (184 mg, 76%) as colorless oil: IR (neat) 2959 (s), 2931 (s), 2853 (s), 1692 (s), 1458 (s), 1039 (s), 965 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 1.17-1.31 (m, 5H), 1.54 (dt, *J* = 14.2, 6.9 Hz, 2H), 1.65 (d, *J* = 6.4 Hz, 3H), 2.46-2.55 (m, 3H), 2.88 (dt, *J* = 6.9, 1.8 Hz, 2H), 5.19 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.43 (dq, *J* = 12.8, 6.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.0, 17.8, 21.8, 22.6, 28.5, 29.2, 31.6, 34.5, 40.1, 49.9, 125.7, 133.4, 198.7; mass spectrum *m/z* (relative intensity) EI 242 (0.35, M^+), 153 (9), 152 (17), 135 (4), 125 (12), 111 (40), 95 (8), 83 (14), 82 (34), 69 (100), 67 (12), 57 (20), 55 (60). HRMS (EI) calculated for $[C_{14}H_{26}OS]^+$: 242.1704, found 242.1705.

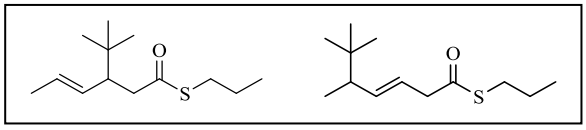
(*E*) *n*-Propyl 3-(1-methylethyl)-4-hexenylthionate (101b). Employing general procedure E and



using thiodienoate **100** (180 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ^{i}PrMgCl (0.60 mL, 2.0 M in Et_2O, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave

101b (156 mg, 73%) as colorless oil. IR (neat) 2951 (s), 2937 (s), 2863 (s), 1697 (s), 1452 (s), 1254 (s), 1034 (s), 953 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3H), 0.88 (d, J =6.9 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H), 1.54-1.62 (m, 3H), 1.65 (d, J = 6.4 Hz, 3H), 2.37-2.43 (m, 1H), 2.51 (dd, J = 9.2, 13. 8 Hz, 1H), 2.61 (dd, J = 5.5, 14.2 Hz, 1H), 2.79-2.88 (m, 2H), 5.23 (dd, J = 8.7, 15.1 Hz, 1H), 5.42 (dt, J = 1.4, 12.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 17.9, 18.7, 20.4, 23.0, 30.7, 31.5, 46.2, 47.3, 126.9, 130.6, 190.1; mass spectrum *m/z* (relative intensity) EI 214 (0.61 M^+), 171 (2), 139 (39), 138 (64), 110 (42), 97 (100), 81 (12), 55 (93).

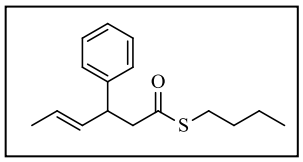
(*E*) *n*-Propyl 3-(2,2dimethylethyl)-4-hexenylthionate (101c) and ***(E) n*-Propyl 5,6,6-trimethyl-3-heptenylthionate (102c)** Employing



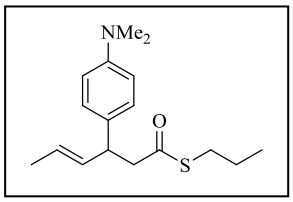
General procedure E and using thioester **100** (180 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ^{t}BuMgCl (0.71 mL, 1.7 M in THF, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2: petroleum ether, v/v) gave the mixture of **101c** and **102c** (180 mg, 79%, 1,4:1.6; 73:27), as colorless oil. IR (neat) 2928 (s), 2931 (s), 2866 (s), 1699 (s), 1443 (s), 1039 (s), 947 (s) cm^{-1}; **Major (101c):** ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 9H), 0.95 (d, J = 5.1 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.54-1.64 (m, 2H), 1.91-1.97 (m, 1H), 2.83 (t, J = 7.4 Hz, 2H), 3.23 (d, J = 6.9 Hz, 2H), 5.48 (dt, J = 14.2, 6.9 Hz, 1H), 5.57 (dd, J = 15.1, 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 15.2, 22.9, 27.4, 30.8, 33.0, 47.2, 47.8, 120.8, 139.7, 198.5; mass spectrum *m/z* (relative intensity) EI 228 (0.52, M^+), 172 (80), 137 (9), 129 (9), 109 (10), 97 (93), 96 (92), 69 (97(, 68 (99), 57 (100); HRMS (EI) calculated for $[C_{13}H_{24}OS]^+$: 228.1548, found 228.1548. **Minor (102c):** ^1H NMR (500 MHz, $CDCl_3$) 0.87 (s, 9H), 0.91-0.98 (m, 6H), 1.26-1.30 (m, 1H), 1.54-1.64 (m, 2H), 2.29-2.34 (m, 1H), 2.40-2.45 (m, 1H), 2.67 (dd, J = 14.2, 3.2 Hz, 1H), 2.79-2.83 (m, 1H), 5.21-5.27 (m, 1H), 5.37-5.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 17.9, 23.0, 27.5, 30.7, 32.9, 45.2,

50.6, 127.5, 130.1, 199.4; mass spectrum *m/z* (relative intensity) EI 228 (0.28, M^+), 213 (3), 172 (30), 152 (50), 137 (13), 124 (12), 111 (62), 97 (70), 96 (54), 69 (100), 57 (97).

(*E*) *n*-Butyl 3-phenyl-4-hexenylthionate (98d). Employing general procedure E and using thioester **97** (184 mg, 1.0 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) and PhMgBr (0.48 mL in Et_2O, 1.2 mmol) in Et_2O after purification by flash column chromatography (silica, 10-20% CH_2Cl_2: petroleum ether, v/v) gave **98d** (204 mg, 76%) as colorless oil. IR (neat) 2963 (s), 2923 (s), 2874 (s), 1687 (s), 1443 (s), 1043 (s), 709 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, J = 7.3 Hz, 3H), 1.20-1.28 (m, 2H), 1.37-1.43 (m, 2H), 1.57 (d, J = 6.4 Hz, 3H), 2.73-2.88 (m, 4H), 3.80 (q, J = 7.3 Hz, 1H), 5.38-5.52 (m, 2H), 7.11-7.23 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 17.9, 21.7, 28.6, 31.5, 45.3, 50.0, 125.9, 126.5, 127.4, 128.5, 132.6, 143.0, 197.9; mass spectrum *m/z* (relative intensity) EI 262 (0.71, M^+), 172 (21), 145 (13), 144 (39), 132 (11), 131 (100), 129 (25), 115 (9), 91 (24), 77 (5). HRMS (EI) calculated for $[C_{16}H_{22}OS]^+$: 262.1391, found 262.1392.

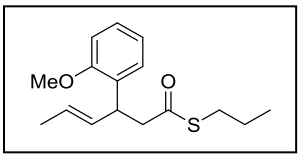


(*E*) *n*-Propyl 3-(4-*N*,*N*-dimethylphenylamino)-4-hexenylthionate (101e). 4-*N*,*N*-dimethylphylamino magnesium bromide used for the reaction was prepared in situ from the reaction of 4-bromo-*N*,*N*-dimethylaniline (240 mg, 1.2 mmol) with magnesium (115 mg, 4.8 mmol) under argon using literature procedure. Employing general procedure E and using thioester **100** (180 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 4-$Me_2NC_6H_4MgBr$ (1.2 mL, 1.0 M in THF, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2: petroleum ether, v/v) gave **101e** (172mg, 59%) as colorless oil. IR (neat) 2934 (s), 2873 (s), 1687 (s), 1456 (s), 1041 (s), 943 (s), 739 (s) cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 0.69 (t, J = 7.3 Hz, 3H), 1.31-1.43 (m, 2H), 1.50 (d, J = 6.4 Hz, 2H), 2.49 (d, J = 6H), 2.47-2.56 (m, 1H), 2.62-2.71 (m, 2H),

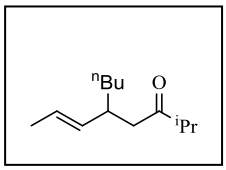


2.88 (d, J = 7.4 Hz, 2H), 4.03 (d, J = 7.4 Hz, 1H), 5.41 (dt, J = 15.2, 8.3 Hz, 1H), 5.59 (dd, J = 15.6, 7.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ 13.0, 17.8, 23.1, 30.7, 40.4, 44.6, 50.5, 113.3, 124.8, 128.3, 131.5, 134.1, 149.3, 196.6; mass spectrum *m/z* (relative intensity) EI 293 (3.12 M^++2), 292 (9.82 M^++1), 291 (44.65, M^+), 187 (12), 174 (100), 159 (22), 144 (14), 132 (10), 118 (6), 91 (4), 79 (4), 65 (2). HRMS (EI) calculated for $[C_{17}H_{25}NOS]^+$: 291.1657, found 291.1655.

***(E)-n*-Propyl 3-(2-methoxyphenyl)-4-hexenylthionate (101f).** The 2-methoxyphenyl magnesium iodide used for the reaction was prepared in situ from the reaction of 2-iodoanisole with magnesium under argon employing literature procedure.[72] Employing General procedure E and using thioester **100** (180 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and 2-$MeOC_6H_4MgI$ (1.2 mL, 1.0 M in THF, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave **101f** (142 mg, 51%) as colorless oil. IR (neat) 2933 (s), 2871 (s), 1693 (s), 1447 (s), 1047 (s), 946 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4Hz, 3H), 1.32 (d, J = 6.9 Hz, 3H), 1.50-1.68 (m, 2H), 2.30-2.44 (m, 2H), 3.34 (dt, J = 15.2, 7.4 Hz, 1H), 3.76 (t, J = 7.4 Hz, 2H), 3.93 (s, 3H), 5.41 (dd, J = 15.6, 9.2 Hz, 1H), 5.67 (dt, J = 14.7, 6.9 Hz, 1H), 6.97-7.02 (m, 2H), 7.47 (t, J = 6.9 Hz ,1H), 7.70 (d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 20.6, 22.9, 32.6, 41.9, 46.9, 55.4, 111.4, 120.7, 123.1, 127.9, 130.6, 133.5, 136.1, 158.5, 200.3; mass spectrum *m/z* (relative intensity) EI 278 (2.37 M^+), 235 (5), 203 (13), 187 (22), 135 (100), 121 (4), 92 (13), 77 (31), 67 (8).

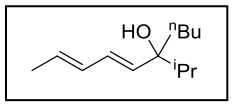


(*E*) 1-Ethylmethyl-3-(1-propenyl)-heptanone (104a). Employing general procedure E and using ketodiene **103** (154 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20%



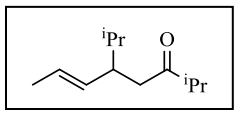
CH_2Cl_2:petroleum ether, v/v) gave the mxixture of **104a** (172 mg, 88%) and **106a** (6 mg, 3%) as colorless oil: IR (neat) 2967 (s), 2933 (s), 2876 (s), 1710 (s), 1458 (s), 1061 (s), 966 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 1.06 (d, J = 4.6 Hz, 6H), 1.18-1.21 (m, 2H), 1.62 (d, J = 6.4 Hz, 3H), 2.38-2.44 (m, 2H), 2.48-2.59 (m, 1H), 5.15-5.23 (m, 1H), 5.23-5.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8 (2-carbon), 17.9, 18.7, 20.4, 31.6, 41.1, 43.7, 44.6, 126.2, 131.7, 214.5; mass spectrum *m/z* (relative intensity) EI 196 (8.0, M^+), 167 (7), 153 (37), 139 (16), 125 (8), 111 (31), 95 (8), 71 (100), 69 (97), 65 (71). HRMS (EI) calculated for $[C_{13}H_{24}O]^+$: 196.1827, found 196.1823.

(*6E, 8E*) 5-(1-Methylethyl)-6,8-decadiene-5-ol (106a): ^1H NMR (500 MHz, $CDCl_3$) δ 0.85-0.93



(m, 9H), 1.23-1.34 (m, 6H), 1.50-1.56 (m, 1H), 1.71-1.75 (m, 1H), 1.77 (d, J = 6.4 Hz, 3H), 5.54 (d, J = 15.6 Hz, 1H), 5.65-5.71 (m, 1H), 6.08 (t, J =14.7 Hz, 1H), 6.16-6.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.5, 17.6, 18.1, 23.2, 25.6, 36.7, 38.5, 128.4, 128.7, 131.2, 135.3.

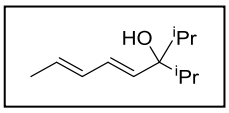
(*E*) 1-Ethylmethyl 3-(1-methylethyl)-4-hexenone (104b). Employing general procedure E and



using ketodiene **103** (154 mg, 1.0 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ^{i}PrMgCl (0.60 mL, 2.0 M in Et_2O, 1.2 mmol) in THF after purification by flash column chromatography (silica, 10-20% CH_2Cl_2:petroleum ether, v/v) gave the mixture of **104b**, **105b** (**104b**:**105b**; 83:17; 140 mg, 77%) and **106b** (7 mg, 4%) as colorless oil. IR (neat) 2964 (s), 2874 (s), 1709 (s), 1655 (s), 1459 (s), 1367 (s), 970 (s) cm^{-1}; **104b:** ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.4 Hz, 6H), 1.11 (t, J = 7.3 Hz, 1H), 1.63 (d, J = 6.0 Hz, 3H), 2.36-2.42 (m, 1H), 2.44 (d, J = 6.4 Hz, 2H), 2.54-2.60 (m, 1H), 5.17-5.24 (m, 1H), 5.35-5.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 18.0, 18.8, 20.5, 31.7, 41.2, 43.7, 44.6, 126.3, 131.7, 214.5; mass spectrum *m/z* (relative intensity) EI 182 (4, M^+),

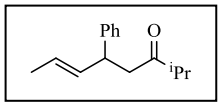
139 (34), 111 (11), 97 (75), 96 (46), 71 (99), 69 (39), 55 (60). HRMS (EI) calculated for $[C_{12}H_{22}O]^+$: 182.1671, found 182.1673.

(*4E, 6E*) 2-Methyl-3-(1-methylethyl)-4,6-octadiene-3-ol 106b: ^{1}H NMR (500 MHz, $CDCl_3$) δ



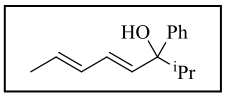
0.75-0.83 (m, 12H), 0.95-0.98 (m, 1H), 1.69 (d, J = 6.0 Hz, 3H), 1.80-1.85 (m, 2H), 5.36 (d, J = 15.6 Hz, 1H), 5.57-5.63 (m, 1H), 6.00-6.12 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 17.6, 18.2, 33.5, 79.4, 128.2, 129.8, 131.3, 133.5.

(*E*) 1-Methylethyl 3-phenyl-4-hexenone (104c). Employing general procedure E and using



ketodiene **103** (184 mg, 1.0 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol) and PhMgBr (0.48 mL in Et_2O, 1.2 mmol) in Et_2O after purification by flash column chromatography (silica, 10-20% CH_2Cl_2: petroleum ether, v/v) gave the mixture of **104c** (132 mg, 61 %) and **106c** (65 mg, 30%) as a colorless oil. IR (neat) 2963 (s), 2932 (s), 2872 (s), 1717 (s), 1686 (s), 1458 (s), 1063 (s), 969 (s), 707 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.56 (d, J = 6.4 Hz, 3H), 2.41 (sept, J = 6.9 Hz, 1H), 2.70-2.79 (m, 2H), 3.80 (q, J = 7.4 Hz, 1H), 5.34-5.53 (m, 2H), 7.06-7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 17.8, 17.9, 41.3, 43.6, 46.6, 125.3, 126.3, 127.5, 128.4, 133.5, 144.0, 212.8; mass spectrum *m/z* (relative intensity) EI 216 (8.0, M^+), 187 (34), 173 (83), 145 (19), 131 (100), 115 (23), 103 (10), 91 (62), 77 (12), 71 (96), 65 (81). HRMS (EI) calculated for $[C_{15}H_{20}O]^+$: 216.1514, found 216.1515.

(*4E, 6E*) 2-Methyl-3-phenyl-4,6-octadiene-3-ol (106c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (d, J



= 6.9 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H), 1.52 (s, 1H), 1.67 (d, J = 6.4 Hz, 3H), 2.10 (sept, J =6.4 Hz, 1H), 5.57-5.63 (m, 1H), 5.90 (d, J = 15.6 Hz, 1H), 6.02 (t, J = 14.7 Hz, 1H), 6.16-6.21 (m, 1H), 7.11-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 17.3, 18.2, 37.9, 79.1, 125.6, 126.6, 128.1, 128.8, 129.5, 131.1, 136.0, 146.1.

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APPENDICES

Appendix A: Crystallographic Information Files

Crystallographic Information File for 69a (Chapter II)

_audit_creation_method	SHELXL-97
_chemical_name_systematic	?
_chemical_name_common	?
_chemical_melting_point	?
_chemical_formula_moiety	?
_chemical_formula_sum	'$C_{15}H_{22}O_3S$'
_chemical_formula_weight	282.39

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
'C' 'C' 0.0033 0.0016
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H' 0.0000 0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'O' 'O' 0.0106 0.0060
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'S' 'S' 0.1246 0.1234
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_cell_setting	Orthorhombic
_symmetry_space_group_name_H-M	P2(1)2(1)2(1)

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
'-x+1/2, -y, z+1/2'
 '-x, y+1/2, -z+1/2'
 'x+1/2, -y+1/2, -z'

_cell_length_a	5.6271(16)
_cell_length_b	13.257(4)
_cell_length_c	20.571(7)
_cell_angle_alpha	90.00
_cell_angle_beta	90.00
_cell_angle_gamma	90.00
_cell_volume	1534.6(9)
_cell_formula_units_Z	4
_cell_measurement_temperature	178(2)
_cell_measurement_reflns_used	4443
_cell_measurement_theta_min	3.7541
_cell_measurement_theta_max	26.3910
_exptl_crystal_description	needle

_exptl_crystal_colour colorless
_exptl_crystal_size_max 0.70
_exptl_crystal_size_mid 0.05
_exptl_crystal_size_min 0.05
_exptl_crystal_density_meas ?
_exptl_crystal_density_diffrn 1.222
_exptl_crystal_density_method 'not measured'
_exptl_crystal_F_000 608
_exptl_absorpt_coefficient_mu 0.213
_exptl_absorpt_correction_type multi-scan
_exptl_absorpt_correction_T_min 0.8654
_exptl_absorpt_correction_T_max 0.9894
_exptl_absorpt_process_details 'Jacobson, R., (1998)'

_diffrn_ambient_temperature 178(2)
_diffrn_radiation_wavelength 0.71073
_diffrn_radiation_type MoK\a
_diffrn_radiation_source 'Sealed Tube'
_diffrn_radiation_monochromator 'Graphite Monochromator'
_diffrn_radiation_detector 'CCD'
_diffrn_measurement_device Mercury 1K CCD
_diffrn_detector_area_resol_mean 14.9365
_diffrn_measurement_method 'omega'
_diffrn_reflns_reduction_process 'Lp corrections applied'
_diffrn_measurement_details

scan:
Number of images: 260
Slice: - 40.0000 - 90.0000
Image width: 0.5000
Exp time: 45.0000
Rotation axis: Omega
Omega: 0.0000
Chi: 45.0000
Phi: 0.0000
XTD: 27.0801
2theta: -0.0260
scan:
Number of images: 220
Slice: -30.0000 - 80.0000
Image width: 0.5000
Exp time: 45.0000
Rotation axis: Omega
Omega: 0.0000
Chi: 45.0000
Phi: 90.0000
XTD: 27.0801
2theta: -0.0260

_diffrn_measurement_device_details

AFC8: Eulerian 3 circle

_diffrn_standards_number	0
_diffrn_standards_interval_count	0
_diffrn_standards_interval_time	0
_diffrn_standards_decay_%	0
_diffrn_reflns_number	12308
_diffrn_reflns_av_R_equivalents	0.0836
_diffrn_reflns_av_sigmaI/netI	0.0697
_diffrn_reflns_limit_h_min	-7
_diffrn_reflns_limit_h_max	6
_diffrn_reflns_limit_k_min	-16
_diffrn_reflns_limit_k_max	15
_diffrn_reflns_limit_l_min	-25
_diffrn_reflns_limit_l_max	25
_diffrn_reflns_theta_min	3.07
_diffrn_reflns_theta_max	26.38
_reflns_number_total	3128
_reflns_number_gt	2424
_reflns_threshold_expression	>2sigma(I)
_computing_data_collection	'CrystalClear (Rigaku/MSC,2006)'
_computing_cell_refinement	'CrystalClear (Rigaku/MSC,2006)'
_computing_data_reduction	'CrystalClear (Rigaku/MSC,2006)'
_computing_structure_solution	'SHELXTL 6.10 (Sheldrick,2008)'
_computing_structure_refinement	'SHELXTL 6.10 (Sheldrick,2008)'
_computing_molecular_graphics	'SHELXTL 6.10 (Sheldrick,2008)'
_computing_publication_material	'SHELXTL 6.10 (Sheldrick,2008)'

_refine_special_details

Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

_refine_ls_structure_factor_coef	Fsqd
_refine_ls_matrix_type	full
_refine_ls_weighting_scheme	calc

_refine_ls_weighting_details

'calc w=1/[\s^2^(Fo^2^)+(0.0872P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3'

_atom_sites_solution_primary	direct
_atom_sites_solution_secondary	difmap
_atom_sites_solution_hydrogens	geom
_refine_ls_hydrogen_treatment	constr
_refine_ls_extinction_method	none

_refine_ls_extinction_coef ?
_refine_ls_abs_structure_details
'Flack H D (1983), Acta Cryst. A39, 876-881'
_refine_ls_abs_structure_Flack 0.44(14)
_refine_ls_number_reflns 3128
_refine_ls_number_parameters 175
_refine_ls_number_restraints 0
_refine_ls_R_factor_all 0.0792
_refine_ls_R_factor_gt 0.0582
_refine_ls_wR_factor_ref 0.1600
_refine_ls_wR_factor_gt 0.1419
_refine_ls_goodness_of_fit_ref 1.028
_refine_ls_restrained_S_all 1.028
_refine_ls_shift/su_max 0.000
_refine_ls_shift/su_mean 0.000

loop_
_atom_site_label
_atom_site_type_symbol
_atom_site_fract_x
_atom_site_fract_y
_atom_site_fract_z
_atom_site_U_iso_or_equiv
_atom_site_adp_type
_atom_site_occupancy
_atom_site_symmetry_multiplicity
_atom_site_calc_flag
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_atom_site_disorder_assembly
_atom_site_disorder_group

S1 S 0.46313(15) 0.17378(7) 0.19354(4) 0.0310(2) Uani 1 1 d . . .
O1 O 0.7110(4) 0.1496(2) 0.20099(14) 0.0407(7) Uani 1 1 d . . .
O2 O 0.3852(6) 0.2746(2) 0.20971(14) 0.0421(7) Uani 1 1 d . . .
O3 O 0.6498(5) -0.0448(2) 0.36881(13) 0.0420(7) Uani 1 1 d . . .
H3 H 0.6447 -0.0952 0.3449 0.050 Uiso 1 1 calc R . .
C1 C 0.2871(7) 0.0893(3) 0.23705(18) 0.0319(8) Uani 1 1 d . . .
H1 H 0.1207 0.1051 0.2356 0.038 Uiso 1 1 calc R . .
C2 C 0.3617(7) 0.0334(3) 0.29910(18) 0.0325(8) Uani 1 1 d . . .
H2 H 0.2338 0.0216 0.3291 0.039 Uiso 1 1 calc R . .
C3 C 0.3377(7) -0.0225(3) 0.23602(18) 0.0314(8) Uani 1 1 d . . .
H3A H 0.4859 -0.0405 0.2161 0.038 Uiso 1 1 calc R . .
C4 C 0.1349(7) -0.0942(3) 0.22155(19) 0.0354(8) Uani 1 1 d . . .
H4A H -0.0057 -0.0714 0.2435 0.043 Uiso 1 1 calc R . .
H4B H 0.1736 -0.1600 0.2379 0.043 Uiso 1 1 calc R . .
C5 C 0.0862(7) -0.1009(3) 0.14924(18) 0.0360(9) Uani 1 1 d . . .
H5A H 0.0520 -0.0345 0.1332 0.043 Uiso 1 1 calc R . .
H5B H 0.2275 -0.1242 0.1278 0.043 Uiso 1 1 calc R . .

C6 C -0.1172(7) -0.1701(4) 0.13127(19) 0.0419(9) Uani 1 1 d . . .
H6A H -0.0856 -0.2362 0.1482 0.050 Uiso 1 1 calc R . .
H6B H -0.2600 -0.1457 0.1514 0.050 Uiso 1 1 calc R . .
C7 C -0.1572(9) -0.1778(4) 0.0589(2) 0.0533(11) Uani 1 1 d . . .
H7A H -0.1793 -0.1115 0.0411 0.080 Uiso 1 1 calc R . .
H7B H -0.2962 -0.2178 0.0506 0.080 Uiso 1 1 calc R . .
H7C H -0.0217 -0.2089 0.0389 0.080 Uiso 1 1 calc R . .
C8 C 0.6030(7) 0.0437(3) 0.33112(18) 0.0349(9) Uani 1 1 d . . .
H8 H 0.7234 0.0516 0.2985 0.042 Uiso 1 1 calc R . .
C9 C 0.6124(9) 0.1318(3) 0.3781(2) 0.0496(12) Uani 1 1 d . . .
H9A H 0.4882 0.1248 0.4098 0.074 Uiso 1 1 calc R . .
H9B H 0.5914 0.1937 0.3546 0.074 Uiso 1 1 calc R . .
H9C H 0.7637 0.1325 0.3997 0.074 Uiso 1 1 calc R . .
C10 C 0.3835(6) 0.1491(3) 0.11194(17) 0.0300(8) Uani 1 1 d . . .
C11 C 0.5354(8) 0.0899(3) 0.07451(19) 0.0405(9) Uani 1 1 d . . .
H11 H 0.6809 0.0640 0.0923 0.049 Uiso 1 1 calc R . .
C12 C 0.4700(9) 0.0693(3) 0.0104(2) 0.0498(11) Uani 1 1 d . . .
H12 H 0.5743 0.0307 -0.0169 0.060 Uiso 1 1 calc R . .
C13 C 0.2557(9) 0.1042(4) -0.0144(2) 0.0493(11) Uani 1 1 d . . .
H13 H 0.2098 0.0875 -0.0581 0.059 Uiso 1 1 calc R . .
C14 C 0.1090(7) 0.1628(4) 0.0236(2) 0.0441(10) Uani 1 1 d . . .
H14 H -0.0374 0.1880 0.0060 0.053 Uiso 1 1 calc R . .
C15 C 0.1715(7) 0.1857(3) 0.08753(19) 0.0362(9) Uani 1 1 d . . .
H15 H 0.0690 0.2263 0.1141 0.043 Uiso 1 1 calc R . .
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_atom_site_aniso_U_11
_atom_site_aniso_U_22
_atom_site_aniso_U_33
_atom_site_aniso_U_23
_atom_site_aniso_U_13
_atom_site_aniso_U_12

S1 0.0334(4) 0.0294(4) 0.0301(4) 0.0015(4) -0.0014(3) -0.0032(4)
O1 0.0284(13) 0.0559(18) 0.0378(15) 0.0051(13) -0.0047(11) -0.0060(12)
O2 0.0577(19) 0.0261(13) 0.0424(17) -0.0036(11) -0.0010(13) -0.0004(12)
O3 0.0574(18) 0.0349(15) 0.0338(15) 0.0036(12) -0.0082(13) 0.0037(14)
C1 0.0304(19) 0.035(2) 0.0306(19) 0.0000(15) -0.0005(14) 0.0013(15)
C2 0.0370(19) 0.0313(18) 0.0291(19) 0.0022(16) 0.0024(15) 0.0037(15)
C3 0.034(2) 0.0310(19) 0.0293(19) 0.0002(14) 0.0013(14) -0.0030(15)
C4 0.040(2) 0.0262(18) 0.040(2) 0.0037(16) -0.0003(16) -0.0031(16)
C5 0.038(2) 0.0323(19) 0.038(2) 0.0035(16) -0.0054(16) -0.0047(17)
C6 0.038(2) 0.047(2) 0.041(2) -0.007(2) 0.0025(16) -0.0060(19)
C7 0.061(3) 0.058(3) 0.040(2) -0.007(2) -0.0089(19) -0.012(3)
C8 0.037(2) 0.033(2) 0.035(2) 0.0033(16) -0.0025(15) 0.0002(16)
C9 0.068(3) 0.035(2) 0.046(3) -0.0104(19) -0.015(2) 0.000(2)
C10 0.0253(17) 0.039(2) 0.0258(18) 0.0057(15) -0.0010(13) -0.0061(14)
C11 0.043(2) 0.043(2) 0.035(2) 0.0001(17) -0.0037(17) 0.005(2)

C12 0.066(3) 0.049(2) 0.035(2) -0.0052(19) -0.001(2) 0.009(2)
C13 0.058(3) 0.055(3) 0.035(2) 0.002(2) -0.007(2) -0.007(2)
C14 0.041(2) 0.051(3) 0.041(2) 0.009(2) -0.0129(17) -0.001(2)
C15 0.0302(19) 0.041(2) 0.037(2) 0.0101(18) -0.0003(14) -0.0022(18)

_geom_special_details
All esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken
into account individually in the estimation of esds in distances, angles
and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell esds is used for estimating esds involving l.s. planes.

loop_
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_geom_bond_atom_site_label_2
_geom_bond_distance
_geom_bond_site_symmetry_2
_geom_bond_publ_flag
S1 O1 1.439(3) . ?
S1 O2 1.446(3) . ?
S1 C1 1.743(4) . ?
S1 C10 1.768(4) . ?
O3 C8 1.432(5) . ?
O3 H3 0.8299 . ?
C1 C3 1.509(5) . ?
C1 C2 1.535(5) . ?
C1 H1 0.9600 . ?
C2 C3 1.500(5) . ?
C2 C8 1.515(5) . ?
C2 H2 0.9600 . ?
C3 C4 1.515(5) . ?
C3 H3A 0.9600 . ?
C4 C5 1.515(5) . ?
C4 H4A 0.9600 . ?
C4 H4B 0.9600 . ?
C5 C6 1.513(5) . ?
C5 H5A 0.9600 . ?
C5 H5B 0.9600 . ?
C6 C7 1.509(6) . ?
C6 H6A 0.9600 . ?
C6 H6B 0.9600 . ?
C7 H7A 0.9599 . ?
C7 H7B 0.9599 . ?
C7 H7C 0.9599 . ?
C8 C9 1.516(5) . ?
C8 H8 0.9600 . ?
C9 H9A 0.9599 . ?

C9 H9B 0.9599 . ?
C9 H9C 0.9599 . ?
C10 C15 1.382(5) . ?
C10 C11 1.392(5) . ?
C11 C12 1.397(6) . ?
C11 H11 0.9600 . ?
C12 C13 1.389(6) . ?
C12 H12 0.9600 . ?
C13 C14 1.376(7) . ?
C13 H13 0.9600 . ?
C14 C15 1.395(6) . ?
C14 H14 0.9600 . ?
C15 H15 0.9600 . ?

loop_
 _geom_angle_atom_site_label_1
 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
O1 S1 O2 118.38(18) . . ?
O1 S1 C1 110.67(18) . . ?
O2 S1 C1 107.68(18) . . ?
O1 S1 C10 107.80(18) . . ?
O2 S1 C10 108.23(18) . . ?
C1 S1 C10 102.96(17) . . ?
C8 O3 H3 109.5 . . ?
C3 C1 C2 59.1(2) . . ?
C3 C1 S1 121.1(3) . . ?
C2 C1 S1 125.6(3) . . ?
C3 C1 H1 113.5 . . ?
C2 C1 H1 113.5 . . ?
S1 C1 H1 113.5 . . ?
C3 C2 C8 120.1(3) . . ?
C3 C2 C1 59.6(2) . . ?
C8 C2 C1 124.3(3) . . ?
C3 C2 H2 114.0 . . ?
C8 C2 H2 114.0 . . ?
C1 C2 H2 114.0 . . ?
C2 C3 C1 61.3(3) . . ?
C2 C3 C4 123.2(3) . . ?
C1 C3 C4 118.5(3) . . ?
C2 C3 H3A 114.5 . . ?
C1 C3 H3A 114.5 . . ?
C4 C3 H3A 114.5 . . ?
C3 C4 C5 111.5(3) . . ?

C3 C4 H4A 109.3 . . ?
C5 C4 H4A 109.3 . . ?
C3 C4 H4B 109.3 . . ?
C5 C4 H4B 109.3 . . ?
H4A C4 H4B 108.0 . . ?
C6 C5 C4 114.4(3) . . ?
C6 C5 H5A 108.7 . . ?
C4 C5 H5A 108.7 . . ?
C6 C5 H5B 108.7 . . ?
C4 C5 H5B 108.7 . . ?
H5A C5 H5B 107.6 . . ?
C7 C6 C5 113.3(3) . . ?
C7 C6 H6A 108.9 . . ?
C5 C6 H6A 108.9 . . ?
C7 C6 H6B 108.9 . . ?
C5 C6 H6B 108.9 . . ?
H6A C6 H6B 107.7 . . ?
C6 C7 H7A 109.5 . . ?
C6 C7 H7B 109.5 . . ?
H7A C7 H7B 109.5 . . ?
C6 C7 H7C 109.5 . . ?
H7A C7 H7C 109.5 . . ?
H7B C7 H7C 109.5 . . ?
O3 C8 C2 109.0(3) . . ?
O3 C8 C9 106.2(3) . . ?
C2 C8 C9 112.2(3) . . ?
O3 C8 H8 109.8 . . ?
C2 C8 H8 109.8 . . ?
C9 C8 H8 109.8 . . ?
C8 C9 H9A 109.5 . . ?
C8 C9 H9B 109.5 . . ?
H9A C9 H9B 109.5 . . ?
C8 C9 H9C 109.5 . . ?
H9A C9 H9C 109.5 . . ?
H9B C9 H9C 109.5 . . ?
C15 C10 C11 121.8(4) . . ?
C15 C10 S1 119.9(3) . . ?
C11 C10 S1 118.3(3) . . ?
C10 C11 C12 118.1(4) . . ?
C10 C11 H11 121.0 . . ?
C12 C11 H11 121.0 . . ?
C13 C12 C11 120.7(4) . . ?
C13 C12 H12 119.7 . . ?
C11 C12 H12 119.7 . . ?
C14 C13 C12 120.0(4) . . ?
C14 C13 H13 120.0 . . ?
C12 C13 H13 120.0 . . ?
C13 C14 C15 120.5(4) . . ?

C13 C14 H14 119.8 . . ?
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C10 S1 C1 C3 71.6(3) . . . . ?
O1 S1 C1 C2 28.8(4) . . . . ?
O2 S1 C1 C2 -102.0(3) . . . . ?
C10 S1 C1 C2 143.8(3) . . . . ?
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S1 C1 C2 C8 -0.5(5) . . . . ?
C8 C2 C3 C1 -114.5(4) . . . . ?
C8 C2 C3 C4 138.6(4) . . . . ?
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C2 C1 C3 C4 114.4(4) . . . . ?
S1 C1 C3 C4 -130.1(3) . . . . ?
C2 C3 C4 C5 153.1(4) . . . . ?
C1 C3 C4 C5 80.4(4) . . . . ?
C3 C4 C5 C6 -179.1(3) . . . . ?
C4 C5 C6 C7 -178.3(4) . . . . ?
C3 C2 C8 O3 -84.2(4) . . . . ?
C1 C2 C8 O3 -155.9(3) . . . . ?
C3 C2 C8 C9 158.4(4) . . . . ?
C1 C2 C8 C9 86.6(5) . . . . ?
O1 S1 C10 C15 -166.0(3) . . . . ?
O2 S1 C10 C15 -36.8(4) . . . . ?
C1 S1 C10 C15 77.0(3) . . . . ?
O1 S1 C10 C11 16.0(4) . . . . ?
O2 S1 C10 C11 145.1(3) . . . . ?
C1 S1 C10 C11 -101.1(3) . . . . ?
C15 C10 C11 C12 1.0(6) . . . . ?
S1 C10 C11 C12 179.1(3) . . . . ?
C10 C11 C12 C13 -2.1(7) . . . . ?

C11 C12 C13 C14 2.3(7) . . . . ?
C12 C13 C14 C15 -1.4(7) . . . . ?
C11 C10 C15 C14 -0.1(6) . . . . ?
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C13 C14 C15 C10 0.3(6) . . . . ?

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Crystallographic Information File for 70e (Chapter II)

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_chemical_name_common	?
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'H' 'H' 0.0000 0.0000
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_symmetry_space_group_name_H-M	P2(1)/c

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 '-x, -y, -z'
 'x, -y-1/2, z-1/2'

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_cell_angle_beta	102.85(3)
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_computing_data_reduction	'CrystalClear (Rigaku/MSC, 2006)'
_computing_structure_solution	'SHELXS-97 (Sheldrick, 1990)'
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_refine_special_details
Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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_refine_ls_weighting_scheme	calc

_refine_ls_weighting_details
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_atom_sites_solution_primary	direct
_atom_sites_solution_secondary	difmap
_atom_sites_solution_hydrogens	geom
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_refine_ls_number_reflns	5564
_refine_ls_number_parameters	363
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_refine_ls_wR_factor_gt	0.2033
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N2 N -0.0593(3) 0.8042(4) 0.2722(5) 0.0521(15) Uani 1 1 d . . .
C20 C -0.0093(3) 0.7444(5) 0.2783(6) 0.0444(15) Uani 1 1 d . . .
C21 C 0.0349(3) 0.7234(4) 0.4088(5) 0.0393(14) Uani 1 1 d . . .
H21 H 0.0167 0.7336 0.4866 0.047 Uiso 1 1 calc R . .
C22 C -0.1018(3) 0.8261(6) 0.1475(6) 0.063(2) Uani 1 1 d . . .
H22A H -0.0918 0.7840 0.0812 0.076 Uiso 1 1 calc R . .
H22B H -0.0933 0.8903 0.1232 0.076 Uiso 1 1 calc R . .
C23 C -0.1726(3) 0.8165(6) 0.1510(8) 0.066(2) Uani 1 1 d . . .
H23A H -0.2000 0.8347 0.0666 0.079 Uiso 1 1 calc R . .
H23B H -0.1822 0.7511 0.1671 0.079 Uiso 1 1 calc R . .
C24 C -0.1889(4) 0.8765(6) 0.2548(8) 0.077(3) Uani 1 1 d . . .
H24A H -0.2347 0.8663 0.2595 0.093 Uiso 1 1 calc R . .
H24B H -0.1837 0.9425 0.2340 0.093 Uiso 1 1 calc R . .
C25 C -0.1436(4) 0.8533(7) 0.3856(7) 0.072(2) Uani 1 1 d . . .
H25A H -0.1523 0.7894 0.4107 0.087 Uiso 1 1 calc R . .
H25B H -0.1527 0.8960 0.4521 0.087 Uiso 1 1 calc R . .
C26 C -0.0714(4) 0.8620(5) 0.3782(7) 0.0593(19) Uani 1 1 d . . .
H26A H -0.0612 0.9275 0.3635 0.071 Uiso 1 1 calc R . .
H26B H -0.0431 0.8418 0.4606 0.071 Uiso 1 1 calc R . .
C27 C 0.1079(3) 0.7425(4) 0.4223(5) 0.0415(15) Uani 1 1 d . . .
H27 H 0.1205 0.7669 0.3436 0.050 Uiso 1 1 calc R . .
C28 C 0.0835(3) 0.6434(5) 0.4138(6) 0.0455(16) Uani 1 1 d . . .
H28 H 0.0819 0.6127 0.3291 0.055 Uiso 1 1 calc R . .
C29 C 0.1446(3) 0.7822(5) 0.5481(6) 0.0486(16) Uani 1 1 d . . .
H29 H 0.1276 0.7544 0.6200 0.058 Uiso 1 1 calc R . .
O4 O 0.2124(2) 0.7522(4) 0.5589(4) 0.0602(13) Uani 1 1 d . . .
H4 H 0.2355 0.7718 0.6281 0.090 Uiso 1 1 calc R . .
C30 C 0.1398(4) 0.8871(5) 0.5541(7) 0.067(2) Uani 1 1 d . . .
H30A H 0.1668 0.9093 0.6355 0.100 Uiso 1 1 calc R . .
H30B H 0.0945 0.9050 0.5485 0.100 Uiso 1 1 calc R . .
H30C H 0.1552 0.9145 0.4822 0.100 Uiso 1 1 calc R . .
C31 C 0.0986(3) 0.5787(5) 0.5285(6) 0.0466(16) Uani 1 1 d . . .
C32 C 0.1568(3) 0.5313(5) 0.5572(7) 0.0573(19) Uani 1 1 d . . .
H32 H 0.1888 0.5432 0.5091 0.069 Uiso 1 1 calc R . .
C33 C 0.1693(4) 0.4657(5) 0.6567(8) 0.067(2) Uani 1 1 d . . .
H33 H 0.2084 0.4306 0.6721 0.081 Uiso 1 1 calc R . .
C34 C 0.1254(4) 0.4525(5) 0.7313(7) 0.065(2) Uani 1 1 d . . .
H34 H 0.1349 0.4094 0.8003 0.078 Uiso 1 1 calc R . .
C18 C 0.0673(4) 0.5005(6) 0.7085(7) 0.066(2) Uani 1 1 d . . .
H18 H 0.0369 0.4917 0.7612 0.079 Uiso 1 1 calc R . .
C19 C 0.0545(4) 0.5628(5) 0.6049(7) 0.0577(18) Uani 1 1 d . . .
H19 H 0.0143 0.5952 0.5866 0.069 Uiso 1 1 calc R . .
O1 O 0.5204(2) 0.2930(4) 0.3440(4) 0.0633(14) Uani 1 1 d . . .
C7 C 0.6224(3) 0.4167(5) 0.0878(7) 0.0558(19) Uani 1 1 d . . .
C8 C 0.5740(4) 0.4447(6) -0.0171(8) 0.070(2) Uani 1 1 d . . .
H8 H 0.5314 0.4201 -0.0286 0.085 Uiso 1 1 calc R . .
C9 C 0.5882(5) 0.5091(6) -0.1057(9) 0.084(3) Uani 1 1 d . . .
H9 H 0.5547 0.5276 -0.1765 0.101 Uiso 1 1 calc R . .

C10 C 0.6493(5) 0.5459(6) -0.0922(10) 0.082(3) Uani 1 1 d . . .
H10 H 0.6583 0.5896 -0.1524 0.098 Uiso 1 1 calc R . .
C11 C 0.6971(5) 0.5182(6) 0.0097(11) 0.090(3) Uani 1 1 d . . .
H11 H 0.7396 0.5427 0.0189 0.108 Uiso 1 1 calc R . .
C12 C 0.6849(4) 0.4540(6) 0.1019(9) 0.075(2) Uani 1 1 d . . .
H12 H 0.7187 0.4365 0.1725 0.090 Uiso 1 1 calc R . .
C3 C 0.6078(3) 0.3520(5) 0.1898(6) 0.0569(19) Uani 1 1 d . . .
H3 H 0.6052 0.3830 0.2725 0.068 Uiso 1 1 calc R . .
C1 C 0.5608(3) 0.2720(5) 0.1518(6) 0.0469(16) Uani 1 1 d . . .
H1 H 0.5437 0.2615 0.0576 0.056 Uiso 1 1 calc R . .
C2 C 0.6331(3) 0.2548(5) 0.2044(6) 0.0506(17) Uani 1 1 d . . .
H2 H 0.6450 0.2312 0.2948 0.061 Uiso 1 1 calc R . .
C5 C 0.6721(3) 0.2149(6) 0.1149(6) 0.0555(18) Uani 1 1 d . . .
H5 H 0.6581 0.2448 0.0286 0.067 Uiso 1 1 calc R . .
O2 O 0.7402(2) 0.2358(4) 0.1673(5) 0.0692(15) Uani 1 1 d . . .
H2A H 0.7440 0.2639 0.2374 0.104 Uiso 1 1 calc R . .
C6 C 0.6643(5) 0.1108(6) 0.0997(9) 0.082(3) Uani 1 1 d . . .
H6A H 0.6925 0.0879 0.0448 0.122 Uiso 1 1 calc R . .
H6B H 0.6189 0.0960 0.0603 0.122 Uiso 1 1 calc R . .
H6C H 0.6766 0.0812 0.1844 0.122 Uiso 1 1 calc R . .
C4 C 0.5144(3) 0.2514(5) 0.2402(6) 0.0494(16) Uani 1 1 d . . .
N1 N 0.4682(3) 0.1853(5) 0.2036(5) 0.0593(17) Uani 1 1 d . . .
C13 C 0.4607(4) 0.1252(6) 0.0905(7) 0.066(2) Uani 1 1 d . . .
H13A H 0.4710 0.0605 0.1181 0.079 Uiso 1 1 calc R . .
H13B H 0.4912 0.1447 0.0371 0.079 Uiso 1 1 calc R . .
C14 C 0.3910(4) 0.1312(7) 0.0119(8) 0.084(3) Uani 1 1 d . . .
H14A H 0.3824 0.1946 -0.0231 0.101 Uiso 1 1 calc R . .
H14B H 0.3852 0.0877 -0.0615 0.101 Uiso 1 1 calc R . .
C15 C 0.3427(4) 0.1078(8) 0.0943(9) 0.092(3) Uani 1 1 d . . .
H15A H 0.3486 0.0425 0.1226 0.110 Uiso 1 1 calc R . .
H15B H 0.2978 0.1151 0.0425 0.110 Uiso 1 1 calc R . .
C16 C 0.3525(4) 0.1708(6) 0.2118(10) 0.082(3) Uani 1 1 d . . .
H16A H 0.3426 0.2357 0.1844 0.099 Uiso 1 1 calc R . .
H16B H 0.3229 0.1522 0.2675 0.099 Uiso 1 1 calc R . .
C17 C 0.4223(3) 0.1630(6) 0.2850(7) 0.068(2) Uani 1 1 d . . .
H17A H 0.4296 0.2056 0.3596 0.082 Uiso 1 1 calc R . .
H17B H 0.4305 0.0991 0.3184 0.082 Uiso 1 1 calc R . .

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N2 0.057(3) 0.063(4) 0.033(3) -0.005(3) 0.002(3) 0.016(3)

C20 0.043(4) 0.058(4) 0.030(3) 0.002(3) 0.005(3) 0.000(3)
C21 0.035(3) 0.056(4) 0.027(3) 0.003(3) 0.007(2) 0.002(3)
C22 0.050(4) 0.100(6) 0.035(4) -0.001(4) 0.000(3) 0.018(4)
C23 0.053(4) 0.079(6) 0.063(5) -0.001(4) 0.005(4) 0.007(4)
C24 0.067(5) 0.097(7) 0.067(5) 0.015(5) 0.014(4) 0.037(5)
C25 0.062(5) 0.101(7) 0.054(5) 0.007(4) 0.013(4) 0.028(5)
C26 0.068(5) 0.061(5) 0.046(4) -0.008(3) 0.007(3) 0.007(4)
C27 0.044(3) 0.054(4) 0.026(3) 0.000(3) 0.007(3) -0.007(3)
C28 0.055(4) 0.053(4) 0.029(3) -0.003(3) 0.012(3) 0.007(3)
C29 0.040(3) 0.069(5) 0.035(3) 0.001(3) 0.004(3) 0.001(3)
O4 0.036(2) 0.101(4) 0.043(3) -0.010(3) 0.0052(19) -0.002(2)
C30 0.071(5) 0.062(5) 0.058(5) -0.009(4) -0.004(4) -0.007(4)
C31 0.047(4) 0.053(4) 0.036(3) -0.007(3) 0.001(3) 0.006(3)
C32 0.050(4) 0.065(5) 0.053(4) 0.002(4) 0.004(3) 0.009(4)
C33 0.070(5) 0.059(5) 0.067(5) 0.003(4) 0.002(4) 0.019(4)
C34 0.084(6) 0.055(5) 0.050(4) 0.005(4) 0.001(4) 0.010(4)
C18 0.072(5) 0.073(6) 0.052(5) 0.007(4) 0.011(4) 0.003(4)
C19 0.061(4) 0.056(5) 0.055(4) 0.009(4) 0.012(4) 0.005(4)
O1 0.064(3) 0.088(4) 0.041(3) -0.009(3) 0.017(2) -0.023(3)
C7 0.051(4) 0.056(5) 0.063(5) -0.018(4) 0.018(4) -0.009(3)
C8 0.065(5) 0.075(6) 0.069(5) 0.005(5) 0.010(4) -0.017(4)
C9 0.107(8) 0.077(6) 0.065(6) 0.002(5) 0.011(5) -0.013(6)
C10 0.107(8) 0.069(6) 0.074(6) 0.005(5) 0.030(6) -0.013(6)
C11 0.088(7) 0.069(6) 0.126(9) 0.001(6) 0.052(7) -0.024(5)
C12 0.056(5) 0.082(6) 0.085(6) 0.001(5) 0.011(4) -0.014(4)
C3 0.060(4) 0.070(5) 0.040(4) -0.013(4) 0.009(3) -0.013(4)
C1 0.044(4) 0.067(5) 0.030(3) -0.003(3) 0.008(3) -0.010(3)
C2 0.040(3) 0.079(5) 0.031(3) 0.002(3) 0.004(3) -0.005(4)
C5 0.048(4) 0.080(5) 0.037(4) 0.000(3) 0.006(3) 0.000(4)
O2 0.039(2) 0.111(4) 0.051(3) -0.005(3) -0.006(2) -0.004(3)
C6 0.095(7) 0.076(6) 0.075(6) 0.003(5) 0.022(5) 0.012(5)
C4 0.048(4) 0.065(5) 0.037(3) 0.000(3) 0.012(3) -0.001(3)
N1 0.053(3) 0.086(5) 0.043(3) -0.012(3) 0.021(3) -0.023(3)
C13 0.062(5) 0.078(6) 0.058(5) -0.008(4) 0.016(4) -0.017(4)
C14 0.088(6) 0.095(7) 0.059(5) 0.009(5) -0.005(5) -0.028(5)
C15 0.054(5) 0.131(9) 0.079(6) 0.033(6) -0.012(4) -0.034(5)
C16 0.053(5) 0.071(6) 0.128(9) 0.018(6) 0.029(5) 0.004(4)
C17 0.057(5) 0.090(6) 0.063(5) -0.015(4) 0.025(4) -0.023(4)

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All esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken
into account individually in the estimation of esds in distances, angles
and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell esds is used for estimating esds involving l.s. planes.
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N2 C20 1.340(8) . ?
N2 C22 1.449(8) . ?
N2 C26 1.459(8) . ?
C20 C21 1.508(8) . ?
C21 C27 1.522(8) . ?
C21 C28 1.522(8) . ?
C21 H21 0.9900 . ?
C22 C23 1.494(9) . ?
C22 H22A 0.9800 . ?
C22 H22B 0.9800 . ?
C23 C24 1.488(10) . ?
C23 H23A 0.9800 . ?
C23 H23B 0.9800 . ?
C24 C25 1.526(10) . ?
C24 H24A 0.9800 . ?
C24 H24B 0.9800 . ?
C25 C26 1.531(10) . ?
C25 H25A 0.9800 . ?
C25 H25B 0.9800 . ?
C26 H26A 0.9800 . ?
C26 H26B 0.9800 . ?
C27 C29 1.490(8) . ?
C27 C28 1.502(9) . ?
C27 H27 0.9900 . ?
C28 C31 1.500(8) . ?
C28 H28 0.9900 . ?
C29 O4 1.460(7) . ?
C29 C30 1.506(9) . ?
C29 H29 0.9900 . ?
O4 H4 0.8300 . ?
C30 H30A 0.9700 . ?
C30 H30B 0.9700 . ?
C30 H30C 0.9700 . ?
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C31 C19 1.370(9) . ?
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C32 H32 0.9400 . ?
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C33 H33 0.9400 . ?
C34 C18 1.369(10) . ?
C34 H34 0.9400 . ?
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C18 H18 0.9400 . ?

C19 H19 0.9400 . ?
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C7 C8 1.382(10) . ?
C7 C12 1.385(10) . ?
C7 C3 1.502(10) . ?
C8 C9 1.390(11) . ?
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C9 C10 1.359(12) . ?
C9 H9 0.9400 . ?
C10 C11 1.352(13) . ?
C10 H10 0.9400 . ?
C11 C12 1.402(12) . ?
C11 H11 0.9400 . ?
C12 H12 0.9400 . ?
C3 C2 1.484(10) . ?
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C3 H3 0.9900 . ?
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C1 C4 1.515(8) . ?
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C6 H6B 0.9700 . ?
C6 H6C 0.9700 . ?
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N1 C17 1.459(8) . ?
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N2 C22 H22B 109.3 . . ?
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H22A C22 H22B 108.0 . . ?
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C24 C23 H23A 109.5 . . ?
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C22 C23 H23B 109.5 . . ?
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C23 C24 C25 110.1(6) . . ?
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C25 C24 H24B 109.6 . . ?
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C26 C25 H25A 109.5 . . ?
C24 C25 H25B 109.5 . . ?
C26 C25 H25B 109.5 . . ?
H25A C25 H25B 108.1 . . ?
N2 C26 C25 109.5(6) . . ?
N2 C26 H26A 109.8 . . ?
C25 C26 H26A 109.8 . . ?
N2 C26 H26B 109.8 . . ?
C25 C26 H26B 109.8 . . ?
H26A C26 H26B 108.2 . . ?

C29 C27 C28 120.9(5) . . ?
C29 C27 C21 117.2(5) . . ?
C28 C27 C21 60.4(4) . . ?
C29 C27 H27 115.7 . . ?
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C21 C27 H27 115.7 . . ?
C31 C28 C27 121.7(5) . . ?
C31 C28 C21 120.7(5) . . ?
C27 C28 C21 60.4(4) . . ?
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C21 C28 H28 114.5 . . ?
O4 C29 C27 104.8(5) . . ?
O4 C29 C30 111.2(6) . . ?
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C29 O4 H4 109.5 . . ?
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C29 C30 H30B 109.5 . . ?
H30A C30 H30B 109.5 . . ?
C29 C30 H30C 109.5 . . ?
H30A C30 H30C 109.5 . . ?
H30B C30 H30C 109.5 . . ?
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C8 C9 H9 119.3 . . ?
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H6B C6 H6C 109.5 . . ?
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N1 C4 C1 118.4(6) . . ?
C4 N1 C13 126.3(5) . . ?

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C13 C14 H14B 109.5 . . ?
H14A C14 H14B 108.0 . . ?
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H15A C15 H15B 108.1 . . ?
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C7 C3 C1 C4 -140.4(7) . . . . ?
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Crystallographic Information File for 102 (Chapter II)

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_symmetry_space_group_name_H-M          C2/c

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 'x+1/2, y+1/2, z'
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 '-x, -y, -z'
 'x, -y, z-1/2'
 '-x+1/2, -y+1/2, -z'
 'x+1/2, -y+1/2, z-1/2'

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_cell_length_b                          6.7633(13)
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_cell_angle_beta                        94.103(7)
_cell_angle_gamma                       90.00
_cell_volume                            5738(2)
_cell_formula_units_Z                   8
_cell_measurement_temperature           188(2)
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_diffrn_ambient_temperature	188(2)
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_diffrn_measurement_details
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Phi:	0.0000
XTD:	26.9931
2theta:	0.0011

scan:

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2theta:	0.0011

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_diffrn_reflns_number	19088
_diffrn_reflns_av_R_equivalents	0.1125
_diffrn_reflns_av_sigmaI/netI	0.0925
_diffrn_reflns_limit_h_min	-32
_diffrn_reflns_limit_h_max	32
_diffrn_reflns_limit_k_min	-8
_diffrn_reflns_limit_k_max	8
_diffrn_reflns_limit_l_min	-32
_diffrn_reflns_limit_l_max	36
_diffrn_reflns_theta_min	2.94
_diffrn_reflns_theta_max	25.03
_reflns_number_total	5043
_reflns_number_gt	2716
_reflns_threshold_expression	>2sigma(I)

_computing_data_collection	'CrystalClear (Rigaku/MSC,2006)'
_computing_cell_refinement	'CrystalClear (Rigaku/MSC,2006)'
_computing_data_reduction	'CrystalClear (Rigaku/MSC,2006)'
_computing_structure_solution	'SHELXTL 6.10 (Sheldrick,2008)'
_computing_structure_refinement	'SHELXTL 6.10 (Sheldrick,2008)'
_computing_molecular_graphics	'SHELXTL 6.10 (Sheldrick,2008)'
_computing_publication_material	'SHELXTL 6.10 (Sheldrick,2008)'

_refine_special_details

Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

_refine_ls_structure_factor_coef	Fsqd
_refine_ls_matrix_type	full
_refine_ls_weighting_scheme	calc
_refine_ls_weighting_details	

'calc w=1/[\s^2^(Fo^2^)+(0.2000P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary direct
_atom_sites_solution_secondary difmap
_atom_sites_solution_hydrogens geom
_refine_ls_hydrogen_treatment constr
_refine_ls_extinction_method none
_refine_ls_extinction_coef ?
_refine_ls_number_reflns 5043
_refine_ls_number_parameters 363
_refine_ls_number_restraints 0
_refine_ls_R_factor_all 0.1621
_refine_ls_R_factor_gt 0.1071
_refine_ls_wR_factor_ref 0.3373
_refine_ls_wR_factor_gt 0.2764
_refine_ls_goodness_of_fit_ref 1.034
_refine_ls_restrained_S_all 1.034
_refine_ls_shift/su_max 0.000
_refine_ls_shift/su_mean 0.000

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_atom_site_disorder_group

O1 O 0.09156(15) 0.4700(5) 0.20917(12) 0.0487(9) Uani 1 1 d . . .
O2 O 0.06653(15) 0.7774(5) 0.19307(13) 0.0531(10) Uani 1 1 d . . .
O3 O 0.11313(18) 0.2568(7) 0.35871(15) 0.0696(12) Uani 1 1 d . . .
O4 O 0.07777(19) 0.4172(7) 0.40782(14) 0.0679(12) Uani 1 1 d . . .
O5 O 0.00854(18) 1.0618(6) 0.37509(16) 0.0693(12) Uani 1 1 d . . .
O6 O 0.00684(17) 1.1753(6) 0.31008(17) 0.0650(12) Uani 1 1 d . . .
O7 O 0.18429(14) -0.0609(5) 0.08061(13) 0.0505(10) Uani 1 1 d . . .
O8 O 0.19323(17) -0.3604(6) 0.11171(18) 0.0757(15) Uani 1 1 d . . .
O9 O 0.37055(19) 0.0233(7) -0.01890(19) 0.0827(16) Uani 1 1 d . . .
O10 O 0.30553(16) 0.1886(6) -0.01018(15) 0.0622(11) Uani 1 1 d . . .
O11 O 0.39702(17) -0.6058(7) 0.05082(16) 0.0711(13) Uani 1 1 d . . .
O12 O 0.34041(17) -0.7351(6) 0.08684(16) 0.0646(12) Uani 1 1 d . . .
N1 N 0.09014(18) 0.3989(7) 0.37144(17) 0.0543(12) Uani 1 1 d . . .
N2 N 0.01747(19) 1.0474(7) 0.33733(19) 0.0581(13) Uani 1 1 d . . .

N3 N 0.33135(18) 0.0460(7) -0.00373(16) 0.0535(12) Uani 1 1 d . . .
N4 N 0.35669(19) -0.6034(7) 0.06547(17) 0.0545(12) Uani 1 1 d . . .
C1 C 0.11500(19) 0.2260(7) 0.15963(17) 0.0446(12) Uani 1 1 d . . .
H1 H 0.0947 0.1205 0.1687 0.054 Uiso 1 1 calc R . .
C2 C 0.1462(2) 0.1788(7) 0.12317(18) 0.0453(12) Uani 1 1 d . . .
H2 H 0.1521 0.2873 0.1042 0.054 Uiso 1 1 calc R . .
C3 C 0.16992(19) 0.1969(8) 0.16874(19) 0.0490(13) Uani 1 1 d . . .
H3 H 0.1880 0.3169 0.1742 0.059 Uiso 1 1 calc R . .
C4 C 0.0947(2) 0.4302(7) 0.16303(17) 0.0457(12) Uani 1 1 d . . .
H4A H 0.1157 0.5247 0.1506 0.055 Uiso 1 1 calc R . .
H4B H 0.0631 0.4382 0.1480 0.055 Uiso 1 1 calc R . .
C5 C 0.07664(18) 0.6486(7) 0.21914(18) 0.0433(12) Uani 1 1 d . . .
C6 C 0.07158(18) 0.6726(7) 0.26644(19) 0.0445(12) Uani 1 1 d . . .
C7 C 0.05122(19) 0.8488(7) 0.28053(18) 0.0451(12) Uani 1 1 d . . .
H7 H 0.0439 0.9550 0.2605 0.054 Uiso 1 1 calc R . .
C8 C 0.04178(19) 0.8679(8) 0.3240(2) 0.0488(13) Uani 1 1 d . . .
C9 C 0.0536(2) 0.7236(8) 0.35371(19) 0.0502(13) Uani 1 1 d . . .
H9 H 0.0472 0.7390 0.3836 0.060 Uiso 1 1 calc R . .
C10 C 0.0751(2) 0.5555(8) 0.33914(19) 0.0481(12) Uani 1 1 d . . .
C11 C 0.08417(19) 0.5241(7) 0.29670(19) 0.0486(13) Uani 1 1 d . . .
H11 H 0.0988 0.4032 0.2879 0.058 Uiso 1 1 calc R . .
C12 C 0.1886(2) 0.0211(9) 0.1955(2) 0.0561(14) Uani 1 1 d . . .
H12A H 0.1724 -0.0962 0.1846 0.067 Uiso 1 1 calc R . .
H12B H 0.2228 0.0054 0.1922 0.067 Uiso 1 1 calc R . .
C13 C 0.1809(2) 0.0419(9) 0.2429(2) 0.0573(15) Uani 1 1 d . . .
H13A H 0.1466 0.0525 0.2464 0.069 Uiso 1 1 calc R . .
H13B H 0.1960 0.1619 0.2536 0.069 Uiso 1 1 calc R . .
C14 C 0.2013(3) -0.1303(13) 0.2697(2) 0.078(2) Uani 1 1 d . . .
H14A H 0.1856 -0.2495 0.2593 0.093 Uiso 1 1 calc R . .
H14B H 0.2354 -0.1427 0.2655 0.093 Uiso 1 1 calc R . .
C15 C 0.1952(3) -0.1109(15) 0.3173(2) 0.085(2) Uani 1 1 d . . .
H15A H 0.2122 0.0046 0.3283 0.127 Uiso 1 1 calc R . .
H15B H 0.2083 -0.2259 0.3321 0.127 Uiso 1 1 calc R . .
H15C H 0.1612 -0.0989 0.3219 0.127 Uiso 1 1 calc R . .
C16 C 0.1384(2) -0.0186(7) 0.10114(18) 0.0476(13) Uani 1 1 d . . .
H16 H 0.1324 -0.1188 0.1221 0.057 Uiso 1 1 calc R . .
C17 C 0.0980(2) -0.0156(10) 0.0657(2) 0.0612(15) Uani 1 1 d . . .
H17A H 0.1075 0.0646 0.0421 0.092 Uiso 1 1 calc R . .
H17B H 0.0692 0.0383 0.0768 0.092 Uiso 1 1 calc R . .
H17C H 0.0917 -0.1480 0.0556 0.092 Uiso 1 1 calc R . .
C18 C 0.2073(2) -0.2308(8) 0.08986(19) 0.0485(13) Uani 1 1 d . . .
C19 C 0.25428(18) -0.2432(7) 0.06810(17) 0.0426(11) Uani 1 1 d . . .
C20 C 0.27015(19) -0.0897(7) 0.04266(16) 0.0428(11) Uani 1 1 d . . .
H20 H 0.2512 0.0286 0.0379 0.051 Uiso 1 1 calc R . .
C21 C 0.31451(19) -0.1146(7) 0.02442(17) 0.0426(11) Uani 1 1 d . . .
C22 C 0.3435(2) -0.2779(7) 0.03100(17) 0.0458(12) Uani 1 1 d . . .
H22 H 0.3745 -0.2885 0.0187 0.055 Uiso 1 1 calc R . .
C23 C 0.3259(2) -0.4273(7) 0.05635(17) 0.0446(12) Uani 1 1 d . . .

C24 C 0.2823(2) -0.4137(7) 0.07514(17) 0.0440(11) Uani 1 1 d . . .
H24 H 0.2714 -0.5193 0.0928 0.053 Uiso 1 1 calc R . .

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O1 0.060(2) 0.0416(18) 0.046(2) -0.0025(15) 0.0120(18) 0.0028(16)
O2 0.063(2) 0.0457(19) 0.052(2) 0.0018(17) 0.0158(19) 0.0088(17)
O3 0.070(3) 0.078(3) 0.061(3) 0.006(2) -0.001(2) 0.016(2)
O4 0.082(3) 0.074(3) 0.048(2) 0.002(2) 0.008(2) -0.005(2)
O5 0.068(3) 0.070(3) 0.071(3) -0.018(2) 0.015(2) 0.001(2)
O6 0.070(3) 0.046(2) 0.081(3) -0.007(2) 0.018(2) 0.0048(18)
O7 0.049(2) 0.0484(19) 0.057(2) 0.0081(16) 0.0221(18) 0.0102(15)
O8 0.065(3) 0.050(2) 0.117(4) 0.022(2) 0.036(3) 0.0070(19)
O9 0.071(3) 0.075(3) 0.108(4) 0.027(3) 0.048(3) 0.013(2)
O10 0.060(3) 0.057(2) 0.071(3) 0.021(2) 0.013(2) 0.0106(19)
O11 0.061(3) 0.084(3) 0.069(3) 0.009(2) 0.012(2) 0.031(2)
O12 0.073(3) 0.048(2) 0.073(3) 0.006(2) 0.007(2) 0.0120(19)
N1 0.047(3) 0.061(3) 0.054(3) 0.005(2) 0.003(2) -0.004(2)
N2 0.050(3) 0.058(3) 0.068(3) -0.021(3) 0.014(2) -0.009(2)
N3 0.052(3) 0.055(3) 0.054(3) 0.004(2) 0.013(2) -0.003(2)
N4 0.060(3) 0.045(2) 0.057(3) -0.004(2) 0.000(2) 0.016(2)
C1 0.045(3) 0.042(2) 0.048(3) 0.001(2) 0.012(2) -0.002(2)
C2 0.046(3) 0.042(2) 0.050(3) 0.000(2) 0.014(2) -0.004(2)
C3 0.037(3) 0.055(3) 0.055(3) -0.005(2) 0.008(2) 0.002(2)
C4 0.051(3) 0.044(2) 0.043(3) 0.002(2) 0.010(2) 0.005(2)
C5 0.036(3) 0.038(2) 0.057(3) 0.002(2) 0.010(2) -0.0003(19)
C6 0.031(2) 0.044(2) 0.060(3) -0.003(2) 0.009(2) -0.0004(19)
C7 0.039(3) 0.042(2) 0.054(3) -0.005(2) 0.002(2) -0.006(2)
C8 0.036(3) 0.049(3) 0.061(3) -0.006(2) 0.004(2) -0.004(2)
C9 0.047(3) 0.054(3) 0.051(3) -0.007(2) 0.008(2) -0.010(2)
C10 0.041(3) 0.052(3) 0.051(3) 0.000(2) 0.001(2) -0.010(2)
C11 0.038(3) 0.043(2) 0.065(4) 0.000(2) 0.007(2) 0.001(2)
C12 0.045(3) 0.069(3) 0.055(3) 0.000(3) 0.009(3) 0.010(3)
C13 0.040(3) 0.078(4) 0.054(3) -0.008(3) 0.007(3) 0.007(3)
C14 0.060(4) 0.114(6) 0.059(4) 0.013(4) 0.001(3) 0.029(4)
C15 0.065(4) 0.131(7) 0.059(4) 0.011(4) 0.007(3) 0.016(4)
C16 0.046(3) 0.047(3) 0.052(3) 0.000(2) 0.020(3) 0.002(2)
C17 0.055(3) 0.069(4) 0.061(4) -0.008(3) 0.010(3) 0.000(3)
C18 0.046(3) 0.047(3) 0.053(3) -0.004(2) 0.009(3) -0.003(2)
C19 0.038(3) 0.042(2) 0.048(3) 0.000(2) 0.002(2) 0.0009(19)
C20 0.047(3) 0.043(2) 0.039(3) -0.009(2) 0.010(2) -0.003(2)
C21 0.042(3) 0.041(2) 0.046(3) -0.005(2) 0.008(2) -0.0022(19)

C22 0.048(3) 0.048(3) 0.041(3) -0.009(2) 0.001(2) 0.003(2)
C23 0.046(3) 0.046(2) 0.041(3) -0.003(2) 0.002(2) 0.009(2)
C24 0.050(3) 0.040(2) 0.041(3) 0.001(2) 0.003(2) 0.000(2)

_geom_special_details
All esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken
into account individually in the estimation of esds in distances, angles
and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell esds is used for estimating esds involving l.s. planes.

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O1 C5 1.319(6) . ?
O1 C4 1.460(6) . ?
O2 C5 1.206(6) . ?
O3 N1 1.231(6) . ?
O4 N1 1.204(6) . ?
O5 N2 1.214(7) . ?
O6 N2 1.228(7) . ?
O7 C18 1.334(6) . ?
O7 C16 1.480(6) . ?
O8 C18 1.188(7) . ?
O9 N3 1.216(6) . ?
O10 N3 1.206(6) . ?
O11 N4 1.228(6) . ?
O12 N4 1.214(6) . ?
N1 C10 1.494(7) . ?
N2 C8 1.460(7) . ?
N3 C21 1.486(7) . ?
N4 C23 1.477(6) . ?
C1 C4 1.496(7) . ?
C1 C2 1.500(7) . ?
C1 C3 1.530(8) . ?
C1 H1 0.9600 . ?
C2 C16 1.507(7) . ?
C2 C3 1.514(8) . ?
C2 H2 0.9600 . ?
C3 C12 1.518(8) . ?
C3 H3 0.9600 . ?
C4 H4A 0.9600 . ?
C4 H4B 0.9600 . ?
C5 C6 1.487(8) . ?

C6 C11 1.399(8) . ?
C6 C7 1.400(7) . ?
C7 C8 1.394(8) . ?
C7 H7 0.9600 . ?
C8 C9 1.363(8) . ?
C9 C10 1.372(8) . ?
C9 H9 0.9600 . ?
C10 C11 1.370(8) . ?
C11 H11 0.9600 . ?
C12 C13 1.501(8) . ?
C12 H12A 0.9600 . ?
C12 H12B 0.9600 . ?
C13 C14 1.515(9) . ?
C13 H13A 0.9600 . ?
C13 H13B 0.9600 . ?
C14 C15 1.498(10) . ?
C14 H14A 0.9600 . ?
C14 H14B 0.9600 . ?
C15 H15A 0.9599 . ?
C15 H15B 0.9599 . ?
C15 H15C 0.9599 . ?
C16 C17 1.504(9) . ?
C16 H16 0.9600 . ?
C17 H17A 0.9599 . ?
C17 H17B 0.9599 . ?
C17 H17C 0.9599 . ?
C18 C19 1.502(7) . ?
C19 C20 1.391(7) . ?
C19 C24 1.395(7) . ?
C20 C21 1.391(7) . ?
C20 H20 0.9600 . ?
C21 C22 1.369(7) . ?
C22 C23 1.387(7) . ?
C22 H22 0.9600 . ?
C23 C24 1.372(7) . ?
C24 H24 0.9600 . ?

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C5 O1 C4 116.0(4) . . ?
C18 O7 C16 118.8(4) . . ?
O4 N1 O3 124.4(5) . . ?

O4 N1 C10 117.9(5) . . ?
O3 N1 C10 117.7(5) . . ?
O5 N2 O6 123.3(5) . . ?
O5 N2 C8 117.8(6) . . ?
O6 N2 C8 119.0(5) . . ?
O10 N3 O9 124.4(5) . . ?
O10 N3 C21 118.4(4) . . ?
O9 N3 C21 117.1(5) . . ?
O12 N4 O11 124.7(5) . . ?
O12 N4 C23 117.8(5) . . ?
O11 N4 C23 117.5(5) . . ?
C4 C1 C2 119.1(4) . . ?
C4 C1 C3 118.3(5) . . ?
C2 C1 C3 60.0(4) . . ?
C4 C1 H1 116.0 . . ?
C2 C1 H1 116.0 . . ?
C3 C1 H1 116.0 . . ?
C1 C2 C16 117.2(4) . . ?
C1 C2 C3 61.0(4) . . ?
C16 C2 C3 122.0(5) . . ?
C1 C2 H2 115.2 . . ?
C16 C2 H2 115.2 . . ?
C3 C2 H2 115.2 . . ?
C2 C3 C12 123.4(5) . . ?
C2 C3 C1 59.0(3) . . ?
C12 C3 C1 119.5(5) . . ?
C2 C3 H3 114.5 . . ?
C12 C3 H3 114.5 . . ?
C1 C3 H3 114.5 . . ?
O1 C4 C1 106.7(4) . . ?
O1 C4 H4A 110.4 . . ?
C1 C4 H4A 110.4 . . ?
O1 C4 H4B 110.4 . . ?
C1 C4 H4B 110.4 . . ?
H4A C4 H4B 108.6 . . ?
O2 C5 O1 124.5(5) . . ?
O2 C5 C6 123.0(4) . . ?
O1 C5 C6 112.5(4) . . ?
C11 C6 C7 119.2(5) . . ?
C11 C6 C5 122.9(4) . . ?
C7 C6 C5 117.8(5) . . ?
C8 C7 C6 119.1(5) . . ?
C8 C7 H7 120.5 . . ?
C6 C7 H7 120.5 . . ?
C9 C8 C7 122.1(5) . . ?
C9 C8 N2 119.9(5) . . ?
C7 C8 N2 118.0(5) . . ?
C8 C9 C10 117.4(5) . . ?

C8 C9 H9 121.3 . . ?
C10 C9 H9 121.3 . . ?
C11 C10 C9 123.7(5) . . ?
C11 C10 N1 118.0(5) . . ?
C9 C10 N1 118.3(5) . . ?
C10 C11 C6 118.4(5) . . ?
C10 C11 H11 120.8 . . ?
C6 C11 H11 120.8 . . ?
C13 C12 C3 113.1(5) . . ?
C13 C12 H12A 109.0 . . ?
C3 C12 H12A 109.0 . . ?
C13 C12 H12B 109.0 . . ?
C3 C12 H12B 109.0 . . ?
H12A C12 H12B 107.8 . . ?
C12 C13 C14 112.8(5) . . ?
C12 C13 H13A 109.0 . . ?
C14 C13 H13A 109.0 . . ?
C12 C13 H13B 109.0 . . ?
C14 C13 H13B 109.0 . . ?
H13A C13 H13B 107.8 . . ?
C15 C14 C13 113.9(6) . . ?
C15 C14 H14A 108.8 . . ?
C13 C14 H14A 108.8 . . ?
C15 C14 H14B 108.8 . . ?
C13 C14 H14B 108.8 . . ?
H14A C14 H14B 107.7 . . ?
C14 C15 H15A 109.5 . . ?
C14 C15 H15B 109.5 . . ?
H15A C15 H15B 109.5 . . ?
C14 C15 H15C 109.5 . . ?
H15A C15 H15C 109.5 . . ?
H15B C15 H15C 109.5 . . ?
O7 C16 C17 107.4(4) . . ?
O7 C16 C2 105.5(4) . . ?
C17 C16 C2 113.0(5) . . ?
O7 C16 H16 110.3 . . ?
C17 C16 H16 110.3 . . ?
C2 C16 H16 110.3 . . ?
C16 C17 H17A 109.5 . . ?
C16 C17 H17B 109.5 . . ?
H17A C17 H17B 109.5 . . ?
C16 C17 H17C 109.5 . . ?
H17A C17 H17C 109.5 . . ?
H17B C17 H17C 109.5 . . ?
O8 C18 O7 126.0(5) . . ?
O8 C18 C19 122.6(5) . . ?
O7 C18 C19 111.3(4) . . ?
C20 C19 C24 120.8(5) . . ?

C20 C19 C18 121.7(4) . . ?
C24 C19 C18 117.4(4) . . ?
C21 C20 C19 117.3(5) . . ?
C21 C20 H20 121.3 . . ?
C19 C20 H20 121.3 . . ?
C22 C21 C20 123.8(5) . . ?
C22 C21 N3 118.3(4) . . ?
C20 C21 N3 117.9(4) . . ?
C21 C22 C23 116.6(5) . . ?
C21 C22 H22 121.7 . . ?
C23 C22 H22 121.7 . . ?
C24 C23 C22 122.8(5) . . ?
C24 C23 N4 118.7(5) . . ?
C22 C23 N4 118.5(5) . . ?
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C23 C24 H24 120.7 . . ?
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 _geom_torsion_site_symmetry_4
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C4 C1 C2 C16 -138.9(5) . . . . ?
C3 C1 C2 C16 113.4(6) . . . . ?
C4 C1 C2 C3 107.8(6) . . . . ?
C1 C2 C3 C12 107.0(5) . . . . ?
C16 C2 C3 C12 1.3(7) . . . . ?
C16 C2 C3 C1 -105.7(5) . . . . ?
C4 C1 C3 C2 -109.1(5) . . . . ?
C4 C1 C3 C12 137.5(5) . . . . ?
C2 C1 C3 C12 -113.5(5) . . . . ?
C5 O1 C4 C1 176.7(4) . . . . ?
C2 C1 C4 O1 -148.1(5) . . . . ?
C3 C1 C4 O1 -78.7(5) . . . . ?
C4 O1 C5 O2 -1.2(7) . . . . ?
C4 O1 C5 C6 176.5(4) . . . . ?
O2 C5 C6 C11 -178.8(5) . . . . ?
O1 C5 C6 C11 3.5(7) . . . . ?
O2 C5 C6 C7 4.2(7) . . . . ?
O1 C5 C6 C7 -173.5(4) . . . . ?
C11 C6 C7 C8 -3.2(7) . . . . ?

C5 C6 C7 C8 174.0(5) . . . . ?
C6 C7 C8 C9 2.8(8) . . . . ?
C6 C7 C8 N2 -175.9(5) . . . . ?
O5 N2 C8 C9 0.0(8) . . . . ?
O6 N2 C8 C9 -179.6(5) . . . . ?
O5 N2 C8 C7 178.7(5) . . . . ?
O6 N2 C8 C7 -0.9(7) . . . . ?
C7 C8 C9 C10 -0.6(8) . . . . ?
N2 C8 C9 C10 178.0(5) . . . . ?
C8 C9 C10 C11 -1.3(8) . . . . ?
C8 C9 C10 N1 177.6(5) . . . . ?
O4 N1 C10 C11 -172.6(5) . . . . ?
O3 N1 C10 C11 5.2(7) . . . . ?
O4 N1 C10 C9 8.4(7) . . . . ?
O3 N1 C10 C9 -173.8(5) . . . . ?
C9 C10 C11 C6 0.9(8) . . . . ?
N1 C10 C11 C6 -178.0(5) . . . . ?
C7 C6 C11 C10 1.4(7) . . . . ?
C5 C6 C11 C10 -175.6(5) . . . . ?
C2 C3 C12 C13 -143.5(5) . . . . ?
C1 C3 C12 C13 -73.0(7) . . . . ?
C3 C12 C13 C14 -177.8(6) . . . . ?
C12 C13 C14 C15 178.6(6) . . . . ?
C18 O7 C16 C17 -113.9(6) . . . . ?
C18 O7 C16 C2 125.3(5) . . . . ?
C1 C2 C16 O7 -157.7(5) . . . . ?
C3 C2 C16 O7 -86.5(5) . . . . ?
C1 C2 C16 C17 85.2(6) . . . . ?
C3 C2 C16 C17 156.5(5) . . . . ?
C16 O7 C18 O8 4.3(9) . . . . ?
C16 O7 C18 C19 -176.9(5) . . . . ?
O8 C18 C19 C20 -180.0(6) . . . . ?
O7 C18 C19 C20 1.3(8) . . . . ?
O8 C18 C19 C24 -1.4(9) . . . . ?
O7 C18 C19 C24 179.8(5) . . . . ?
C24 C19 C20 C21 0.6(8) . . . . ?
C18 C19 C20 C21 179.1(5) . . . . ?
C19 C20 C21 C22 -1.7(8) . . . . ?
C19 C20 C21 N3 178.5(5) . . . . ?
O10 N3 C21 C22 178.8(5) . . . . ?
O9 N3 C21 C22 -0.9(8) . . . . ?
O10 N3 C21 C20 -1.4(8) . . . . ?
O9 N3 C21 C20 178.9(5) . . . . ?
C20 C21 C22 C23 2.1(8) . . . . ?
N3 C21 C22 C23 -178.1(5) . . . . ?
C21 C22 C23 C24 -1.6(8) . . . . ?
C21 C22 C23 N4 -178.1(5) . . . . ?
O12 N4 C23 C24 5.0(8) . . . . ?

O11 N4 C23 C24 -174.9(5) . . . . ?
O12 N4 C23 C22 -178.3(5) . . . . ?
O11 N4 C23 C22 1.7(8) . . . . ?
C22 C23 C24 C19 0.7(8) . . . . ?
N4 C23 C24 C19 177.2(5) . . . . ?
C20 C19 C24 C23 -0.2(8) . . . . ?
C18 C19 C24 C23 -178.7(5) . . . . ?

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Crystallographic Information File for 103 (Chapter II)

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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H' 0.0000 0.0000
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'N' 'N' 0.0061 0.0033
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_symmetry_space_group_name_H-M	P-1

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'-x, -y, -z'

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_cell_length_c	19.093(2)
_cell_angle_alpha	73.751(19)
_cell_angle_beta	75.66(2)
_cell_angle_gamma	85.64(2)
_cell_volume	2410.8(6)
_cell_formula_units_Z	4
_cell_measurement_temperature	183(2)
_cell_measurement_reflns_used	4092
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_exptl_crystal_density_meas	'not measured'
_exptl_crystal_density_diffrn	1.313
_exptl_crystal_density_method	'not measured'
_exptl_crystal_F_000	1000
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_exptl_absorpt_process_details	'REQAB, CrystalClear'
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_diffrn_radiation_wavelength	0.71073
_diffrn_radiation_type	MoK\a
_diffrn_radiation_source	'fine-focus sealed tube'
_diffrn_radiation_monochromator	graphite
_diffrn_measurement_device_type	'Rigaku AFC8S'
_diffrn_measurement_method	'\w scans'
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_computing_data_reduction	'CrystalClear (Rigaku/MSC, 2006)'
_computing_structure_solution	'SHELXS-97 (Sheldrick, 1990)'
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_computing_molecular_graphics	'DIAMOND (Bradenburg, 1999)'
_computing_publication_material	'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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_atom_sites_solution_secondary	difmap
_atom_sites_solution_hydrogens	geom
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_refine_ls_number_reflns	8404
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_refine_ls_number_restraints	0
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_refine_ls_R_factor_gt	0.1445
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_refine_ls_wR_factor_gt	0.2687
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_refine_ls_restrained_S_all	1.168
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_refine_ls_shift/su_mean	0.000

loop_
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_atom_site_adp_type
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S1 S 0.8117(3) 0.3037(2) 0.29425(17) 0.0604(7) Uani 1 1 d . . .
O1 O 1.2073(6) 0.1331(6) 0.3926(4) 0.0554(17) Uani 1 1 d . . .
O2 O 1.2057(7) 0.0032(6) 0.4991(4) 0.065(2) Uani 1 1 d . . .
O3 O 1.7460(10) 0.0893(8) 0.1894(6) 0.109(4) Uani 1 1 d . . .
O4 O 1.5697(8) 0.1834(7) 0.1825(4) 0.073(2) Uani 1 1 d . . .
O5 O 1.6047(9) -0.2197(7) 0.5098(5) 0.076(2) Uani 1 1 d . . .
O6 O 1.7675(8) -0.1926(6) 0.4120(5) 0.075(2) Uani 1 1 d . . .
O7 O 0.8990(8) 0.3579(6) 0.2235(4) 0.073(2) Uani 1 1 d . . .
O8 O 0.6843(8) 0.2656(7) 0.2937(6) 0.084(3) Uani 1 1 d . . .
N1 N 1.6335(10) 0.1143(8) 0.2176(6) 0.066(3) Uani 1 1 d . . .
N2 N 1.6557(10) -0.1709(8) 0.4459(7) 0.069(3) Uani 1 1 d . . .
C1 C 0.8909(9) 0.1902(8) 0.3396(6) 0.053(2) Uani 1 1 d . . .
H1 H 0.8387 0.1411 0.3830 0.064 Uiso 1 1 calc R . .
C2 C 1.0302(10) 0.2024(9) 0.3412(6) 0.057(3) Uani 1 1 d . . .
H2 H 1.0664 0.2734 0.3151 0.069 Uiso 1 1 calc R . .
C3 C 1.0037(10) 0.1379(9) 0.2919(6) 0.057(3) Uani 1 1 d . . .
H3 H 1.0245 0.1750 0.2393 0.068 Uiso 1 1 calc R . .
C4 C 1.0638(9) 0.1519(10) 0.4148(6) 0.059(3) Uani 1 1 d . . .
H4 H 1.0198 0.0835 0.4392 0.071 Uiso 1 1 calc R . .
C5 C 1.0367(11) 0.2256(10) 0.4665(6) 0.068(3) Uani 1 1 d . . .
H5A H 1.0837 0.2925 0.4421 0.102 Uiso 1 1 calc R . .
H5B H 1.0636 0.1898 0.5118 0.102 Uiso 1 1 calc R . .
H5C H 0.9456 0.2414 0.4784 0.102 Uiso 1 1 calc R . .
C6 C 1.2613(9) 0.0542(8) 0.4359(6) 0.051(2) Uani 1 1 d . . .
C7 C 1.3963(9) 0.0293(8) 0.4002(5) 0.047(2) Uani 1 1 d . . .
C8 C 1.4535(10) 0.0877(8) 0.3283(6) 0.054(3) Uani 1 1 d . . .
H8 H 1.4081 0.1474 0.3016 0.065 Uiso 1 1 calc R . .
C9 C 1.5775(9) 0.0592(8) 0.2948(6) 0.049(2) Uani 1 1 d . . .
C10 C 1.6459(10) -0.0249(8) 0.3317(6) 0.054(3) Uani 1 1 d . . .
H10 H 1.7311 -0.0447 0.3078 0.065 Uiso 1 1 calc R . .
C11 C 1.5869(9) -0.0798(8) 0.4048(6) 0.049(2) Uani 1 1 d . . .
C12 C 1.4613(10) -0.0577(8) 0.4414(6) 0.053(2) Uani 1 1 d . . .
H12 H 1.4216 -0.0991 0.4914 0.064 Uiso 1 1 calc R . .
C13 C 1.0179(11) 0.0139(10) 0.3098(7) 0.069(3) Uani 1 1 d . . .
H13A H 0.9953 -0.0170 0.3632 0.082 Uiso 1 1 calc R . .
H13B H 0.9595 -0.0145 0.2887 0.082 Uiso 1 1 calc R . .
C14 C 1.1548(15) -0.0188(14) 0.2785(11) 0.116(6) Uani 1 1 d . . .
H14A H 1.1682 -0.0023 0.2249 0.139 Uiso 1 1 calc R . .
H14B H 1.2125 0.0265 0.2885 0.139 Uiso 1 1 calc R . .
C15 C 1.191(2) -0.1288(17) 0.3051(13) 0.147(8) Uani 1 1 d . . .
H15A H 1.1322 -0.1759 0.2979 0.177 Uiso 1 1 calc R . .
H15B H 1.1867 -0.1452 0.3579 0.177 Uiso 1 1 calc R . .
C16 C 1.334(2) -0.151(2) 0.2623(17) 0.212(15) Uani 1 1 d . . .
H16A H 1.3307 -0.1983 0.2314 0.318 Uiso 1 1 calc R . .
H16B H 1.3837 -0.1853 0.2981 0.318 Uiso 1 1 calc R . .
H16C H 1.3730 -0.0831 0.2313 0.318 Uiso 1 1 calc R . .
C17 C 0.7860(12) 0.3884(8) 0.3544(6) 0.060(3) Uani 1 1 d . . .
C18 C 0.8794(13) 0.4709(10) 0.3408(7) 0.075(3) Uani 1 1 d . . .

H18 H 0.9522 0.4813 0.2982 0.090 Uiso 1 1 calc R . .
C19 C 0.8633(16) 0.5357(10) 0.3900(8) 0.086(4) Uani 1 1 d . . .
H19 H 0.9263 0.5902 0.3828 0.103 Uiso 1 1 calc R . .
C20 C 0.758(2) 0.5211(13) 0.4483(10) 0.106(6) Uani 1 1 d . . .
H20 H 0.7451 0.5692 0.4802 0.128 Uiso 1 1 calc R . .
C21 C 0.668(2) 0.4417(15) 0.4640(9) 0.119(6) Uani 1 1 d . . .
H21 H 0.5983 0.4316 0.5080 0.143 Uiso 1 1 calc R . .
C22 C 0.6793(15) 0.3710(11) 0.4131(8) 0.087(4) Uani 1 1 d . . .
H22 H 0.6160 0.3167 0.4208 0.104 Uiso 1 1 calc R . .
S1' S 0.7879(3) 0.3503(2) -0.17108(16) 0.0592(7) Uani 1 1 d . . .
O1' O 0.7349(7) 0.4351(6) 0.0833(4) 0.0559(17) Uani 1 1 d . . .
O2' O 0.8612(8) 0.5657(6) 0.0870(4) 0.067(2) Uani 1 1 d . . .
O3' O 0.3257(8) 0.3463(6) 0.2634(5) 0.070(2) Uani 1 1 d . . .
O4' O 0.2834(8) 0.4089(7) 0.3614(5) 0.079(2) Uani 1 1 d . . .
O5' O 0.6893(12) 0.7674(8) 0.2744(6) 0.113(4) Uani 1 1 d . . .
O6' O 0.5328(9) 0.7014(8) 0.3689(6) 0.091(3) Uani 1 1 d . . .
O7' O 0.8483(9) 0.4010(6) -0.2497(4) 0.079(2) Uani 1 1 d . . .
O8' O 0.6484(7) 0.3284(6) -0.1480(5) 0.068(2) Uani 1 1 d . . .
N1' N 0.3495(10) 0.4050(7) 0.3007(6) 0.062(2) Uani 1 1 d . . .
N2' N 0.6014(13) 0.7005(9) 0.3080(6) 0.088(4) Uani 1 1 d . . .
C1' C 0.8230(11) 0.4311(8) -0.1184(5) 0.052(2) Uani 1 1 d . . .
H1' H 0.9111 0.4546 -0.1301 0.062 Uiso 1 1 calc R . .
C2' C 0.7500(9) 0.4072(8) -0.0367(5) 0.050(2) Uani 1 1 d . . .
H2' H 0.6873 0.3498 -0.0200 0.061 Uiso 1 1 calc R . .
C3' C 0.7181(11) 0.5095(8) -0.0922(6) 0.059(3) Uani 1 1 d . . .
H3' H 0.6383 0.5058 -0.1062 0.071 Uiso 1 1 calc R . .
C4' C 0.8306(9) 0.4103(8) 0.0183(5) 0.050(2) Uani 1 1 d . . .
H4' H 0.8944 0.4669 -0.0038 0.060 Uiso 1 1 calc R . .
C5' C 0.8936(11) 0.3028(9) 0.0484(6) 0.062(3) Uani 1 1 d . . .
H5'1 H 0.9323 0.3080 0.0876 0.094 Uiso 1 1 calc R . .
H5'2 H 0.9593 0.2854 0.0086 0.094 Uiso 1 1 calc R . .
H5'3 H 0.8295 0.2464 0.0680 0.094 Uiso 1 1 calc R . .
C6' C 0.7632(10) 0.5115(8) 0.1116(6) 0.051(2) Uani 1 1 d . . .
C7' C 0.6634(10) 0.5260(8) 0.1750(6) 0.050(2) Uani 1 1 d . . .
C8' C 0.5528(10) 0.4599(8) 0.2063(5) 0.050(2) Uani 1 1 d . . .
H8' H 0.5406 0.4038 0.1839 0.060 Uiso 1 1 calc R . .
C9' C 0.4620(10) 0.4736(8) 0.2680(6) 0.051(2) Uani 1 1 d . . .
C10' C 0.4776(11) 0.5529(9) 0.3039(6) 0.058(3) Uani 1 1 d . . .
H10' H 0.4166 0.5607 0.3485 0.070 Uiso 1 1 calc R . .
C11' C 0.5858(11) 0.6191(9) 0.2711(6) 0.060(3) Uani 1 1 d . . .
C12' C 0.6738(11) 0.6083(8) 0.2081(6) 0.056(3) Uani 1 1 d . . .
H12' H 0.7446 0.6586 0.1861 0.067 Uiso 1 1 calc R . .
C13' C 0.7563(11) 0.6248(8) -0.0975(7) 0.064(3) Uani 1 1 d . . .
H13C H 0.8310 0.6218 -0.0774 0.077 Uiso 1 1 calc R . .
H13D H 0.7779 0.6667 -0.1491 0.077 Uiso 1 1 calc R . .
C14' C 0.6441(12) 0.6789(10) -0.0536(8) 0.075(3) Uani 1 1 d . . .
H14C H 0.6182 0.6339 -0.0029 0.090 Uiso 1 1 calc R . .
H14D H 0.5715 0.6870 -0.0761 0.090 Uiso 1 1 calc R . .

C15' C 0.6853(15) 0.7909(11) -0.0534(11) 0.116(6) Uani 1 1 d . . .
H15C H 0.7167 0.8341 -0.1041 0.140 Uiso 1 1 calc R . .
H15D H 0.7541 0.7824 -0.0279 0.140 Uiso 1 1 calc R . .
C16' C 0.5654(18) 0.8514(13) -0.0122(14) 0.158(9) Uani 1 1 d . . .
H16D H 0.4888 0.8396 -0.0268 0.237 Uiso 1 1 calc R . .
H16E H 0.5823 0.9283 -0.0261 0.237 Uiso 1 1 calc R . .
H16F H 0.5528 0.8227 0.0412 0.237 Uiso 1 1 calc R . .
C17' C 0.8683(10) 0.2259(8) -0.1424(6) 0.053(2) Uani 1 1 d . . .
C18' C 0.8023(12) 0.1415(9) -0.0850(7) 0.069(3) Uani 1 1 d . . .
H18' H 0.7135 0.1500 -0.0602 0.082 Uiso 1 1 calc R . .
C19' C 0.8703(13) 0.0431(10) -0.0644(8) 0.078(4) Uani 1 1 d . . .
H19' H 0.8270 -0.0165 -0.0247 0.093 Uiso 1 1 calc R . .
C20' C 0.9960(12) 0.0304(11) -0.0994(8) 0.072(3) Uani 1 1 d . . .
H20' H 1.0404 -0.0374 -0.0841 0.086 Uiso 1 1 calc R . .
C21' C 1.0591(13) 0.1138(11) -0.1561(8) 0.077(4) Uani 1 1 d . . .
H21' H 1.1471 0.1039 -0.1816 0.093 Uiso 1 1 calc R . .
C22' C 0.9968(11) 0.2126(9) -0.1768(6) 0.064(3) Uani 1 1 d . . .
H22' H 1.0427 0.2722 -0.2153 0.076 Uiso 1 1 calc R . .

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 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
S1 0.0628(18) 0.0518(16) 0.0655(19) -0.0077(13) -0.0234(14) 0.0027(12)
O1 0.033(4) 0.066(5) 0.063(5) -0.015(4) -0.008(3) 0.001(3)
O2 0.054(5) 0.067(5) 0.058(5) -0.003(4) -0.002(4) 0.003(4)
O3 0.102(8) 0.078(6) 0.095(7) 0.003(5) 0.035(6) 0.017(5)
O4 0.069(5) 0.075(6) 0.062(5) -0.006(4) -0.007(4) 0.000(4)
O5 0.080(6) 0.065(5) 0.073(6) -0.001(4) -0.023(5) 0.011(4)
O6 0.059(5) 0.071(5) 0.091(6) -0.023(4) -0.018(5) 0.021(4)
O7 0.085(6) 0.067(5) 0.049(5) 0.004(4) -0.007(4) 0.004(4)
O8 0.065(5) 0.071(5) 0.134(8) -0.031(5) -0.058(5) 0.008(4)
N1 0.060(6) 0.053(6) 0.075(7) -0.016(5) 0.004(5) -0.002(5)
N2 0.070(7) 0.050(6) 0.094(8) -0.017(6) -0.036(6) 0.004(5)
C1 0.044(6) 0.051(6) 0.052(6) 0.002(5) -0.011(5) 0.008(4)
C2 0.045(6) 0.065(7) 0.061(7) -0.012(5) -0.019(5) 0.002(5)
C3 0.043(6) 0.066(7) 0.054(6) -0.012(5) -0.006(5) 0.006(5)
C4 0.029(5) 0.079(8) 0.063(7) -0.012(6) -0.007(5) 0.003(5)
C5 0.058(7) 0.086(9) 0.058(7) -0.016(6) -0.016(6) 0.004(6)
C6 0.040(5) 0.051(6) 0.058(7) -0.011(5) -0.010(5) 0.002(4)
C7 0.046(6) 0.050(6) 0.042(6) -0.007(4) -0.011(4) -0.003(4)
C8 0.048(6) 0.041(5) 0.076(7) -0.015(5) -0.023(5) 0.006(4)
C9 0.038(5) 0.049(6) 0.057(6) -0.013(5) -0.006(5) -0.006(4)
C10 0.040(5) 0.056(6) 0.073(7) -0.030(6) -0.011(5) 0.001(5)

C11 0.045(6) 0.039(5) 0.063(7) -0.013(5) -0.013(5) -0.002(4)
C12 0.055(6) 0.045(6) 0.057(6) -0.011(5) -0.014(5) -0.001(5)
C13 0.058(7) 0.072(8) 0.081(8) -0.030(7) -0.019(6) 0.006(6)
C14 0.099(11) 0.116(13) 0.186(18) -0.102(13) -0.079(12) 0.052(10)
C15 0.16(2) 0.132(17) 0.18(2) -0.067(16) -0.083(18) 0.027(15)
C16 0.124(17) 0.32(3) 0.34(4) -0.28(3) -0.14(2) 0.113(19)
C17 0.086(8) 0.039(6) 0.050(6) -0.007(5) -0.013(6) -0.003(5)
C18 0.085(9) 0.065(8) 0.073(8) -0.015(6) -0.020(7) -0.007(6)
C19 0.121(12) 0.062(8) 0.074(9) -0.026(7) -0.012(9) -0.011(8)
C20 0.170(18) 0.074(10) 0.086(12) -0.035(9) -0.036(12) -0.001(11)
C21 0.145(17) 0.101(13) 0.080(11) -0.012(10) 0.001(11) 0.043(12)
C22 0.087(10) 0.076(9) 0.080(10) -0.010(7) -0.005(8) 0.012(7)
S1' 0.0667(18) 0.0560(16) 0.0614(18) -0.0210(13) -0.0235(14) 0.0074(13)
O1' 0.057(4) 0.059(4) 0.048(4) -0.019(3) 0.001(3) -0.010(3)
O2' 0.071(5) 0.061(5) 0.066(5) -0.024(4) -0.003(4) -0.018(4)
O3' 0.069(5) 0.065(5) 0.073(5) -0.019(4) -0.011(4) -0.011(4)
O4' 0.073(6) 0.084(6) 0.065(6) -0.017(4) 0.016(4) -0.025(4)
O5' 0.144(10) 0.084(7) 0.100(8) -0.051(6) 0.034(7) -0.054(7)
O6' 0.092(7) 0.094(7) 0.096(7) -0.057(6) 0.002(5) -0.021(5)
O7' 0.124(8) 0.071(5) 0.040(4) -0.012(4) -0.018(4) 0.005(5)
O8' 0.053(5) 0.067(5) 0.092(6) -0.031(4) -0.025(4) 0.012(4)
N1' 0.065(6) 0.054(6) 0.066(6) -0.012(5) -0.018(5) 0.005(4)
N2' 0.118(10) 0.074(7) 0.071(7) -0.043(6) 0.009(7) -0.012(7)
C1' 0.059(6) 0.048(6) 0.045(6) -0.017(5) -0.002(5) -0.002(5)
C2' 0.046(6) 0.056(6) 0.045(6) -0.014(5) -0.002(4) -0.004(4)
C3' 0.059(7) 0.054(6) 0.070(7) -0.021(5) -0.021(6) 0.004(5)
C4' 0.047(6) 0.063(6) 0.031(5) -0.013(4) 0.005(4) 0.000(5)
C5' 0.051(6) 0.063(7) 0.058(7) -0.005(5) -0.001(5) 0.009(5)
C6' 0.055(6) 0.047(6) 0.050(6) -0.010(5) -0.014(5) 0.007(5)
C7' 0.053(6) 0.047(6) 0.053(6) -0.013(5) -0.020(5) -0.001(4)
C8' 0.059(6) 0.045(6) 0.051(6) -0.013(5) -0.028(5) 0.009(5)
C9' 0.048(6) 0.054(6) 0.046(6) -0.006(5) -0.010(5) 0.000(5)
C10' 0.064(7) 0.057(7) 0.049(6) -0.009(5) -0.014(5) 0.010(5)
C11' 0.060(7) 0.053(6) 0.068(7) -0.026(6) -0.006(6) 0.001(5)
C12' 0.063(7) 0.043(6) 0.058(7) -0.005(5) -0.016(5) -0.004(5)
C13' 0.067(7) 0.043(6) 0.083(8) -0.021(6) -0.016(6) -0.001(5)
C14' 0.065(8) 0.062(8) 0.095(10) -0.027(7) -0.003(7) -0.006(6)
C15' 0.089(11) 0.068(9) 0.162(16) -0.042(10) 0.034(10) 0.007(8)
C16' 0.114(14) 0.078(11) 0.26(3) -0.091(14) 0.040(15) 0.005(9)
C17' 0.052(6) 0.056(6) 0.052(6) -0.021(5) -0.013(5) 0.012(5)
C18' 0.068(8) 0.050(7) 0.089(9) -0.014(6) -0.028(7) 0.004(5)
C19' 0.084(9) 0.055(7) 0.088(9) -0.013(6) -0.017(7) 0.003(6)
C20' 0.063(8) 0.065(8) 0.084(9) -0.025(7) -0.009(7) 0.010(6)
C21' 0.068(8) 0.080(9) 0.093(10) -0.040(8) -0.022(7) 0.022(7)
C22' 0.067(8) 0.058(7) 0.061(7) -0.013(5) -0.010(6) 0.003(5)

_geom_special_details

All esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken
into account individually in the estimation of esds in distances, angles
and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell esds is used for estimating esds involving l.s. planes.

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S1 O8 1.479(8) . ?
S1 C1 1.741(9) . ?
S1 C17 1.747(10) . ?
O1 C6 1.308(12) . ?
O1 C4 1.501(11) . ?
O2 C6 1.222(12) . ?
O3 N1 1.244(12) . ?
O4 N1 1.221(12) . ?
O5 N2 1.211(12) . ?
O6 N2 1.258(12) . ?
N1 C9 1.438(14) . ?
N2 C11 1.465(13) . ?
C1 C2 1.512(14) . ?
C1 C3 1.547(13) . ?
C1 H1 0.9600 . ?
C2 C4 1.492(14) . ?
C2 C3 1.496(14) . ?
C2 H2 0.9600 . ?
C3 C13 1.524(15) . ?
C3 H3 0.9600 . ?
C4 C5 1.509(15) . ?
C4 H4 0.9600 . ?
C5 H5A 0.9599 . ?
C5 H5B 0.9599 . ?
C5 H5C 0.9599 . ?
C6 C7 1.483(13) . ?
C7 C8 1.376(14) . ?
C7 C12 1.411(13) . ?
C8 C9 1.387(13) . ?
C8 H8 0.9600 . ?
C9 C10 1.374(14) . ?
C10 C11 1.385(14) . ?

C10 H10 0.9600 . ?
C11 C12 1.395(13) . ?
C12 H12 0.9600 . ?
C13 C14 1.507(18) . ?
C13 H13A 0.9600 . ?
C13 H13B 0.9600 . ?
C14 C15 1.41(2) . ?
C14 H14A 0.9600 . ?
C14 H14B 0.9600 . ?
C15 C16 1.58(3) . ?
C15 H15A 0.9600 . ?
C15 H15B 0.9600 . ?
C16 H16A 0.9599 . ?
C16 H16B 0.9599 . ?
C16 H16C 0.9599 . ?
C17 C22 1.365(17) . ?
C17 C18 1.429(16) . ?
C18 C19 1.388(16) . ?
C18 H18 0.9600 . ?
C19 C20 1.36(2) . ?
C19 H19 0.9600 . ?
C20 C21 1.36(2) . ?
C20 H20 0.9600 . ?
C21 C22 1.48(2) . ?
C21 H21 0.9600 . ?
C22 H22 0.9600 . ?
S1' O7' 1.458(8) . ?
S1' O8' 1.467(8) . ?
S1' C1' 1.743(10) . ?
S1' C17' 1.756(10) . ?
O1' C6' 1.324(11) . ?
O1' C4' 1.490(10) . ?
O2' C6' 1.214(12) . ?
O3' N1' 1.244(11) . ?
O4' N1' 1.211(11) . ?
O5' N2' 1.239(13) . ?
O6' N2' 1.213(12) . ?
N1' C9' 1.441(13) . ?
N2' C11' 1.446(13) . ?
C1' C2' 1.516(13) . ?
C1' C3' 1.526(13) . ?
C1' H1' 0.9600 . ?
C2' C3' 1.508(14) . ?
C2' C4' 1.523(13) . ?
C2' H2' 0.9600 . ?
C3' C13' 1.524(13) . ?
C3' H3' 0.9600 . ?
C4' C5' 1.506(14) . ?

C4' H4' 0.9600 . ?
C5' H5'1 0.9599 . ?
C5' H5'2 0.9599 . ?
C5' H5'3 0.9599 . ?
C6' C7' 1.445(14) . ?
C7' C12' 1.390(13) . ?
C7' C8' 1.405(14) . ?
C8' C9' 1.371(13) . ?
C8' H8' 0.9600 . ?
C9' C10' 1.409(14) . ?
C10' C11' 1.389(15) . ?
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C11' C12' 1.364(14) . ?
C12' H12' 0.9600 . ?
C13' C14' 1.519(15) . ?
C13' H13C 0.9600 . ?
C13' H13D 0.9600 . ?
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C14' H14C 0.9600 . ?
C14' H14D 0.9600 . ?
C15' C16' 1.593(18) . ?
C15' H15C 0.9600 . ?
C15' H15D 0.9600 . ?
C16' H16D 0.9599 . ?
C16' H16E 0.9599 . ?
C16' H16F 0.9599 . ?
C17' C22' 1.384(14) . ?
C17' C18' 1.388(15) . ?
C18' C19' 1.407(15) . ?
C18' H18' 0.9600 . ?
C19' C20' 1.360(17) . ?
C19' H19' 0.9600 . ?
C20' C21' 1.363(18) . ?
C20' H20' 0.9600 . ?
C21' C22' 1.381(16) . ?
C21' H21' 0.9600 . ?
C22' H22' 0.9600 . ?

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O7 S1 C1 108.6(5) . . ?

O8 S1 C1 106.8(5) . . ?
O7 S1 C17 108.9(5) . . ?
O8 S1 C17 108.2(6) . . ?
C1 S1 C17 103.7(5) . . ?
C6 O1 C4 119.3(8) . . ?
O4 N1 O3 122.6(11) . . ?
O4 N1 C9 119.2(9) . . ?
O3 N1 C9 118.1(10) . . ?
O5 N2 O6 123.7(10) . . ?
O5 N2 C11 119.6(10) . . ?
O6 N2 C11 116.7(11) . . ?
C2 C1 C3 58.6(6) . . ?
C2 C1 S1 118.4(8) . . ?
C3 C1 S1 118.6(7) . . ?
C2 C1 H1 116.3 . . ?
C3 C1 H1 116.3 . . ?
S1 C1 H1 116.3 . . ?
C4 C2 C3 123.7(10) . . ?
C4 C2 C1 115.7(9) . . ?
C3 C2 C1 61.9(7) . . ?
C4 C2 H2 114.9 . . ?
C3 C2 H2 114.9 . . ?
C1 C2 H2 114.9 . . ?
C2 C3 C13 122.9(9) . . ?
C2 C3 C1 59.5(6) . . ?
C13 C3 C1 119.9(9) . . ?
C2 C3 H3 114.5 . . ?
C13 C3 H3 114.5 . . ?
C1 C3 H3 114.5 . . ?
C2 C4 O1 102.9(8) . . ?
C2 C4 C5 113.5(9) . . ?
O1 C4 C5 109.1(8) . . ?
C2 C4 H4 110.3 . . ?
O1 C4 H4 110.3 . . ?
C5 C4 H4 110.3 . . ?
C4 C5 H5A 109.5 . . ?
C4 C5 H5B 109.5 . . ?
H5A C5 H5B 109.5 . . ?
C4 C5 H5C 109.5 . . ?
H5A C5 H5C 109.5 . . ?
H5B C5 H5C 109.5 . . ?
O2 C6 O1 123.7(9) . . ?
O2 C6 C7 122.7(9) . . ?
O1 C6 C7 113.6(9) . . ?
C8 C7 C12 121.8(9) . . ?
C8 C7 C6 120.3(9) . . ?
C12 C7 C6 117.9(9) . . ?
C7 C8 C9 119.2(9) . . ?

C7 C8 H8 120.4 . . ?
C9 C8 H8 120.4 . . ?
C10 C9 C8 121.9(10) . . ?
C10 C9 N1 118.6(9) . . ?
C8 C9 N1 119.3(9) . . ?
C9 C10 C11 117.4(9) . . ?
C9 C10 H10 121.3 . . ?
C11 C10 H10 121.3 . . ?
C10 C11 C12 123.9(9) . . ?
C10 C11 N2 119.1(10) . . ?
C12 C11 N2 116.9(10) . . ?
C11 C12 C7 115.8(10) . . ?
C11 C12 H12 122.1 . . ?
C7 C12 H12 122.1 . . ?
C14 C13 C3 110.9(11) . . ?
C14 C13 H13A 109.5 . . ?
C3 C13 H13A 109.5 . . ?
C14 C13 H13B 109.5 . . ?
C3 C13 H13B 109.5 . . ?
H13A C13 H13B 108.0 . . ?
C15 C14 C13 117.5(18) . . ?
C15 C14 H14A 107.9 . . ?
C13 C14 H14A 107.9 . . ?
C15 C14 H14B 107.9 . . ?
C13 C14 H14B 107.9 . . ?
H14A C14 H14B 107.2 . . ?
C14 C15 C16 111(2) . . ?
C14 C15 H15A 109.5 . . ?
C16 C15 H15A 109.5 . . ?
C14 C15 H15B 109.5 . . ?
C16 C15 H15B 109.5 . . ?
H15A C15 H15B 108.0 . . ?
C15 C16 H16A 109.5 . . ?
C15 C16 H16B 109.5 . . ?
H16A C16 H16B 109.5 . . ?
C15 C16 H16C 109.5 . . ?
H16A C16 H16C 109.5 . . ?
H16B C16 H16C 109.5 . . ?
C22 C17 C18 123.2(11) . . ?
C22 C17 S1 118.5(10) . . ?
C18 C17 S1 118.3(9) . . ?
C19 C18 C17 119.0(13) . . ?
C19 C18 H18 120.5 . . ?
C17 C18 H18 120.5 . . ?
C20 C19 C18 119.2(14) . . ?
C20 C19 H19 120.4 . . ?
C18 C19 H19 120.4 . . ?
C19 C20 C21 123.4(14) . . ?

C19 C20 H20 118.3 . . ?
C21 C20 H20 118.3 . . ?
C20 C21 C22 119.8(16) . . ?
C20 C21 H21 120.1 . . ?
C22 C21 H21 120.1 . . ?
C17 C22 C21 115.4(15) . . ?
C17 C22 H22 122.3 . . ?
C21 C22 H22 122.3 . . ?
O7' S1' O8' 119.9(5) . . ?
O7' S1' C1' 107.5(5) . . ?
O8' S1' C1' 108.3(5) . . ?
O7' S1' C17' 108.2(5) . . ?
O8' S1' C17' 107.5(5) . . ?
C1' S1' C17' 104.4(5) . . ?
C6' O1' C4' 118.6(8) . . ?
O4' N1' O3' 124.3(10) . . ?
O4' N1' C9' 118.7(9) . . ?
O3' N1' C9' 117.1(10) . . ?
O6' N2' O5' 122.5(10) . . ?
O6' N2' C11' 121.4(12) . . ?
O5' N2' C11' 116.1(10) . . ?
C2' C1' C3' 59.4(6) . . ?
C2' C1' S1' 117.3(8) . . ?
C3' C1' S1' 118.0(8) . . ?
C2' C1' H1' 116.7 . . ?
C3' C1' H1' 116.7 . . ?
S1' C1' H1' 116.7 . . ?
C3' C2' C1' 60.6(7) . . ?
C3' C2' C4' 121.9(9) . . ?
C1' C2' C4' 115.5(8) . . ?
C3' C2' H2' 115.7 . . ?
C1' C2' H2' 115.7 . . ?
C4' C2' H2' 115.7 . . ?
C2' C3' C13' 124.8(9) . . ?
C2' C3' C1' 60.0(6) . . ?
C13' C3' C1' 118.9(9) . . ?
C2' C3' H3' 114.1 . . ?
C13' C3' H3' 114.1 . . ?
C1' C3' H3' 114.1 . . ?
O1' C4' C5' 106.8(8) . . ?
O1' C4' C2' 104.3(7) . . ?
C5' C4' C2' 114.2(9) . . ?
O1' C4' H4' 110.4 . . ?
C5' C4' H4' 110.4 . . ?
C2' C4' H4' 110.4 . . ?
C4' C5' H5'1 109.5 . . ?
C4' C5' H5'2 109.5 . . ?
H5'1 C5' H5'2 109.5 . . ?

C4' C5' H5'3 109.5 . . ?
H5'1 C5' H5'3 109.5 . . ?
H5'2 C5' H5'3 109.5 . . ?
O2' C6' O1' 124.3(9) . . ?
O2' C6' C7' 122.7(9) . . ?
O1' C6' C7' 113.0(9) . . ?
C12' C7' C8' 116.8(10) . . ?
C12' C7' C6' 120.2(10) . . ?
C8' C7' C6' 123.0(9) . . ?
C9' C8' C7' 121.5(9) . . ?
C9' C8' H8' 119.3 . . ?
C7' C8' H8' 119.3 . . ?
C8' C9' C10' 121.2(10) . . ?
C8' C9' N1' 121.5(9) . . ?
C10' C9' N1' 117.2(10) . . ?
C11' C10' C9' 116.4(10) . . ?
C11' C10' H10' 121.8 . . ?
C9' C10' H10' 121.8 . . ?
C12' C11' C10' 122.4(10) . . ?
C12' C11' N2' 121.3(10) . . ?
C10' C11' N2' 116.2(10) . . ?
C11' C12' C7' 121.5(10) . . ?
C11' C12' H12' 119.3 . . ?
C7' C12' H12' 119.3 . . ?
C14' C13' C3' 109.5(9) . . ?
C14' C13' H13C 109.8 . . ?
C3' C13' H13C 109.8 . . ?
C14' C13' H13D 109.8 . . ?
C3' C13' H13D 109.8 . . ?
H13C C13' H13D 108.2 . . ?
C13' C14' C15' 109.8(10) . . ?
C13' C14' H14C 109.7 . . ?
C15' C14' H14C 109.7 . . ?
C13' C14' H14D 109.7 . . ?
C15' C14' H14D 109.7 . . ?
H14C C14' H14D 108.2 . . ?
C14' C15' C16' 110.0(12) . . ?
C14' C15' H15C 109.7 . . ?
C16' C15' H15C 109.7 . . ?
C14' C15' H15D 109.7 . . ?
C16' C15' H15D 109.7 . . ?
H15C C15' H15D 108.2 . . ?
C15' C16' H16D 109.5 . . ?
C15' C16' H16E 109.5 . . ?
H16D C16' H16E 109.5 . . ?
C15' C16' H16F 109.5 . . ?
H16D C16' H16F 109.5 . . ?
H16E C16' H16F 109.5 . . ?

C22' C17' C18' 120.4(10) . . ?
C22' C17' S1' 120.0(9) . . ?
C18' C17' S1' 119.6(8) . . ?
C17' C18' C19' 117.6(12) . . ?
C17' C18' H18' 121.2 . . ?
C19' C18' H18' 121.2 . . ?
C20' C19' C18' 121.5(13) . . ?
C20' C19' H19' 119.3 . . ?
C18' C19' H19' 119.3 . . ?
C19' C20' C21' 120.2(12) . . ?
C19' C20' H20' 119.9 . . ?
C21' C20' H20' 119.9 . . ?
C20' C21' C22' 120.1(12) . . ?
C20' C21' H21' 120.0 . . ?
C22' C21' H21' 120.0 . . ?
C21' C22' C17' 120.2(12) . . ?
C21' C22' H22' 119.9 . . ?
C17' C22' H22' 119.9 . . ?

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 _geom_torsion_site_symmetry_4
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O7 S1 C1 C2 43.6(9) . . . . ?
O8 S1 C1 C2 173.6(8) . . . . ?
C17 S1 C1 C2 -72.2(9) . . . . ?
O7 S1 C1 C3 -24.0(9) . . . . ?
O8 S1 C1 C3 106.0(9) . . . . ?
C17 S1 C1 C3 -139.8(8) . . . . ?
C3 C1 C2 C4 -116.1(11) . . . . ?
S1 C1 C2 C4 136.0(9) . . . . ?
S1 C1 C2 C3 -107.9(9) . . . . ?
C4 C2 C3 C13 -4.4(15) . . . . ?
C1 C2 C3 C13 -108.0(11) . . . . ?
C4 C2 C3 C1 103.6(11) . . . . ?
S1 C1 C3 C2 107.5(9) . . . . ?
C2 C1 C3 C13 112.8(11) . . . . ?
S1 C1 C3 C13 -139.7(9) . . . . ?
C3 C2 C4 O1 84.1(11) . . . . ?
C1 C2 C4 O1 156.2(8) . . . . ?
C3 C2 C4 C5 -158.1(10) . . . . ?

C1 C2 C4 C5 -86.0(12) . . . . ?
C6 O1 C4 C2 -152.9(9) . . . . ?
C6 O1 C4 C5 86.3(11) . . . . ?
C4 O1 C6 O2 -10.5(15) . . . . ?
C4 O1 C6 C7 167.7(8) . . . . ?
O2 C6 C7 C8 178.6(10) . . . . ?
O1 C6 C7 C8 0.4(13) . . . . ?
O2 C6 C7 C12 0.6(14) . . . . ?
O1 C6 C7 C12 -177.5(9) . . . . ?
C12 C7 C8 C9 1.1(14) . . . . ?
C6 C7 C8 C9 -176.8(9) . . . . ?
C7 C8 C9 C10 -0.9(14) . . . . ?
C7 C8 C9 N1 175.1(9) . . . . ?
O4 N1 C9 C10 174.4(9) . . . . ?
O3 N1 C9 C10 -5.7(14) . . . . ?
O4 N1 C9 C8 -1.7(14) . . . . ?
O3 N1 C9 C8 178.2(10) . . . . ?
C8 C9 C10 C11 -1.0(14) . . . . ?
N1 C9 C10 C11 -177.0(9) . . . . ?
C9 C10 C11 C12 2.9(14) . . . . ?
C9 C10 C11 N2 179.2(9) . . . . ?
O5 N2 C11 C10 -179.7(9) . . . . ?
O6 N2 C11 C10 1.4(13) . . . . ?
O5 N2 C11 C12 -3.1(14) . . . . ?
O6 N2 C11 C12 178.0(9) . . . . ?
C10 C11 C12 C7 -2.6(14) . . . . ?
N2 C11 C12 C7 -179.1(8) . . . . ?
C8 C7 C12 C11 0.6(14) . . . . ?
C6 C7 C12 C11 178.5(8) . . . . ?
C2 C3 C13 C14 -87.6(13) . . . . ?
C1 C3 C13 C14 -158.6(11) . . . . ?
C3 C13 C14 C15 165.2(14) . . . . ?
C13 C14 C15 C16 175.8(13) . . . . ?
O7 S1 C17 C22 160.0(10) . . . . ?
O8 S1 C17 C22 28.7(11) . . . . ?
C1 S1 C17 C22 -84.5(11) . . . . ?
O7 S1 C17 C18 -21.6(11) . . . . ?
O8 S1 C17 C18 -152.9(9) . . . . ?
C1 S1 C17 C18 94.0(10) . . . . ?
C22 C17 C18 C19 1.2(19) . . . . ?
S1 C17 C18 C19 -177.2(10) . . . . ?
C17 C18 C19 C20 -2(2) . . . . ?
C18 C19 C20 C21 4(3) . . . . ?
C19 C20 C21 C22 -4(3) . . . . ?
C18 C17 C22 C21 -1.9(19) . . . . ?
S1 C17 C22 C21 176.5(10) . . . . ?
C20 C21 C22 C17 3(2) . . . . ?
O7' S1' C1' C2' 168.8(8) . . . . ?

O8' S1' C1' C2' 37.9(9) . . . . ?
C17' S1' C1' C2' -76.5(9) . . . . ?
O7' S1' C1' C3' 100.7(9) . . . . ?
O8' S1' C1' C3' -30.2(9) . . . . ?
C17' S1' C1' C3' -144.5(8) . . . . ?
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C3' C1' C2' C4' -113.8(10) . . . . ?
S1' C1' C2' C4' 138.2(8) . . . . ?
C1' C2' C3' C13' -106.1(12) . . . . ?
C4' C2' C3' C13' -2.7(15) . . . . ?
C4' C2' C3' C1' 103.4(10) . . . . ?
S1' C1' C3' C2' 106.8(9) . . . . ?
C2' C1' C3' C13' 115.8(11) . . . . ?
S1' C1' C3' C13' -137.5(9) . . . . ?
C6' O1' C4' C5' 105.4(10) . . . . ?
C6' O1' C4' C2' -133.3(9) . . . . ?
C3' C2' C4' O1' 85.3(10) . . . . ?
C1' C2' C4' O1' 155.2(8) . . . . ?
C3' C2' C4' C5' -158.5(9) . . . . ?
C1' C2' C4' C5' -88.6(11) . . . . ?
C4' O1' C6' O2' 2.1(15) . . . . ?
C4' O1' C6' C7' -178.9(8) . . . . ?
O2' C6' C7' C12' 3.4(15) . . . . ?
O1' C6' C7' C12' -175.5(9) . . . . ?
O2' C6' C7' C8' -176.6(10) . . . . ?
O1' C6' C7' C8' 4.4(14) . . . . ?
C12' C7' C8' C9' -2.2(14) . . . . ?
C6' C7' C8' C9' 177.9(9) . . . . ?
C7' C8' C9' C10' -1.6(14) . . . . ?
C7' C8' C9' N1' -179.2(9) . . . . ?
O4' N1' C9' C8' 168.6(9) . . . . ?
O3' N1' C9' C8' -12.5(14) . . . . ?
O4' N1' C9' C10' -9.1(14) . . . . ?
O3' N1' C9' C10' 169.8(9) . . . . ?
C8' C9' C10' C11' 3.0(15) . . . . ?
N1' C9' C10' C11' -179.3(9) . . . . ?
C9' C10' C11' C12' -0.6(16) . . . . ?
C9' C10' C11' N2' 180.0(10) . . . . ?
O6' N2' C11' C12' -170.6(12) . . . . ?
O5' N2' C11' C12' 8.5(19) . . . . ?
O6' N2' C11' C10' 8.8(18) . . . . ?
O5' N2' C11' C10' -172.1(12) . . . . ?
C10' C11' C12' C7' -3.3(17) . . . . ?
N2' C11' C12' C7' 176.1(11) . . . . ?
C8' C7' C12' C11' 4.6(15) . . . . ?
C6' C7' C12' C11' -175.5(10) . . . . ?
C2' C3' C13' C14' -96.1(13) . . . . ?
C1' C3' C13' C14' -167.9(10) . . . . ?

C3' C13' C14' C15' 175.5(12) . . . . ?
C13' C14' C15' C16' 176.2(15) . . . . ?
O7' S1' C17' C22' 27.7(10) . . . . ?
O8' S1' C17' C22' 158.5(8) . . . . ?
C1' S1' C17' C22' -86.6(9) . . . . ?
O7' S1' C17' C18' -152.4(9) . . . . ?
O8' S1' C17' C18' -21.7(10) . . . . ?
C1' S1' C17' C18' 93.3(9) . . . . ?
C22' C17' C18' C19' -0.8(16) . . . . ?
S1' C17' C18' C19' 179.4(9) . . . . ?
C17' C18' C19' C20' -0.2(18) . . . . ?
C18' C19' C20' C21' 0(2) . . . . ?
C19' C20' C21' C22' 1.8(19) . . . . ?
C20' C21' C22' C17' -2.7(18) . . . . ?
C18' C17' C22' C21' 2.2(17) . . . . ?
S1' C17' C22' C21' -177.9(9) . . . . ?

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_diffrn_reflns_theta_full	25.03
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_refine_diff_density_max	0.654
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Crystallographic Information File for 104 (Chapter II)

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_chemical_name_common	?
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'C' 'C' 0.0033 0.0016
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H' 0.0000 0.0000
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'O' 'O' 0.0106 0.0060
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_symmetry_space_group_name_H-M	P2(1)/c

loop_
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 '-x, -y, -z'
 'x, -y-1/2, z-1/2'

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_cell_length_b	16.362(3)
_cell_length_c	10.483(2)
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_cell_angle_beta	104.44(3)
_cell_angle_gamma	90.00
_cell_volume	2284.7(8)
_cell_formula_units_Z	4
_cell_measurement_temperature	203(2)
_cell_measurement_reflns_used	19815
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_exptl_crystal_colour	'colorless'
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_exptl_crystal_size_min	0.33
_exptl_crystal_density_meas	'not measured'
_exptl_crystal_density_diffrn	1.359
_exptl_crystal_density_method	'not measured'
_exptl_crystal_F_000	984
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_diffrn_ambient_temperature	203(2)
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_diffrn_radiation_type	MoK\a
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_diffrn_radiation_monochromator	graphite
_diffrn_measurement_device_type	'Rigaku AFC8S'
_diffrn_measurement_method	'\w scans'
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_diffrn_standards_decay_%	0
_diffrn_reflns_number	19441
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_diffrn_reflns_av_sigmaI/netI	0.0373
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_diffrn_reflns_limit_l_min	-13
_diffrn_reflns_limit_l_max	11
_diffrn_reflns_theta_min	2.49
_diffrn_reflns_theta_max	26.37
_reflns_number_total	4644
_reflns_number_gt	3516
_reflns_threshold_expression	>2sigma(I)

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_computing_cell_refinement	'CrystalClear (Rigaku/MSC, 2006)'
_computing_data_reduction	'CrystalClear (Rigaku/MSC, 2006)'
_computing_structure_solution	'SHELXS-97 (Sheldrick, 1990)'
_computing_structure_refinement	'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics	'DIAMOND (Bradenburg, 1999)'
_computing_publication_material	'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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_refine_ls_matrix_type	full
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_refine_ls_weighting_details	
'calc w=1/[\s^2^(Fo^2^)+(0.0944P)^2^+1.3952P] where P=(Fo^2^+2Fc^2^)/3'	
_atom_sites_solution_primary	direct
_atom_sites_solution_secondary	difmap
_atom_sites_solution_hydrogens	geom
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_refine_ls_extinction_method	none
_refine_ls_extinction_coef	?
_refine_ls_number_reflns	4644
_refine_ls_number_parameters	308
_refine_ls_number_restraints	0
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_refine_ls_R_factor_gt	0.0662
_refine_ls_wR_factor_ref	0.1930
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_refine_ls_goodness_of_fit_ref	1.033
_refine_ls_restrained_S_all	1.033
_refine_ls_shift/su_max	0.000
_refine_ls_shift/su_mean	0.000

loop_
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_atom_site_fract_z
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_atom_site_adp_type
_atom_site_occupancy
_atom_site_symmetry_multiplicity
_atom_site_calc_flag
_atom_site_refinement_flags
_atom_site_disorder_assembly
_atom_site_disorder_group

O1 O 0.86462(13) 0.04065(10) 0.79963(18) 0.0480(4) Uani 1 1 d . . .
O2 O 0.80937(12) 0.09407(9) 0.96729(16) 0.0412(4) Uani 1 1 d . . .
O3 O 0.94283(15) 0.32178(12) 0.86818(17) 0.0565(5) Uani 1 1 d . . .
O4 O 0.55157(14) -0.04176(11) 1.12785(18) 0.0511(5) Uani 1 1 d . . .
N1 N 0.53842(16) -0.09239(13) 1.0390(2) 0.0483(5) Uani 1 1 d . . .
C19 C 0.74064(16) -0.03041(13) 0.8790(2) 0.0372(5) Uani 1 1 d . . .
C24 C 0.67421(17) -0.02871(14) 0.9605(2) 0.0392(5) Uani 1 1 d . . .
H24 H 0.6723 0.0163 1.0156 0.047 Uiso 1 1 calc R . .
C20 C 0.74261(17) -0.09738(14) 0.7990(2) 0.0408(5) Uani 1 1 d . . .
H20 H 0.7865 -0.0988 0.7431 0.049 Uiso 1 1 calc R . .
C21 C 0.67874(18) -0.16214(14) 0.8028(2) 0.0426(5) Uani 1 1 d . . .
C1 C 0.81159(17) 0.03843(13) 0.8756(2) 0.0382(5) Uani 1 1 d . . .
C2 C 0.88144(17) 0.16204(13) 0.9814(2) 0.0392(5) Uani 1 1 d . . .
H2 H 0.8858 0.1814 0.8935 0.047 Uiso 1 1 calc R . .
C22 C 0.61235(18) -0.16319(14) 0.8807(2) 0.0433(5) Uani 1 1 d . . .
H22 H 0.5697 -0.2080 0.8815 0.052 Uiso 1 1 calc R . .
C23 C 0.61124(18) -0.09524(14) 0.9578(2) 0.0415(5) Uani 1 1 d . . .
N2 N 0.68152(18) -0.23303(14) 0.7165(3) 0.0560(6) Uani 1 1 d . . .
C13 C 0.95638(19) 0.33307(14) 0.9872(2) 0.0431(5) Uani 1 1 d . . .
N3 N 1.04457(16) 0.36091(14) 1.0620(2) 0.0489(5) Uani 1 1 d . . .
O5 O 0.46804(17) -0.14006(14) 1.0130(3) 0.0709(6) Uani 1 1 d . . .
C7 C 0.68126(18) 0.32562(14) 1.0090(2) 0.0429(5) Uani 1 1 d . . .
O6 O 0.7286(2) -0.22774(14) 0.6343(3) 0.0798(7) Uani 1 1 d . . .
C5 C 0.77154(18) 0.29306(14) 0.9722(2) 0.0409(5) Uani 1 1 d . . .
H5 H 0.7658 0.2914 0.8762 0.049 Uiso 1 1 calc R . .
C6 C 0.87572(18) 0.31427(14) 1.0553(2) 0.0395(5) Uani 1 1 d . . .
H6 H 0.8786 0.3446 1.1379 0.047 Uiso 1 1 calc R . .
C4 C 0.83678(17) 0.22720(13) 1.0494(2) 0.0395(5) Uani 1 1 d . . .
H4 H 0.8169 0.2088 1.1293 0.047 Uiso 1 1 calc R . .
C3 C 0.9832(2) 0.13388(17) 1.0603(3) 0.0519(6) Uani 1 1 d . . .
H3A H 0.9790 0.1183 1.1480 0.078 Uiso 1 1 calc R . .
H3B H 1.0313 0.1780 1.0665 0.078 Uiso 1 1 calc R . .
H3C H 1.0048 0.0873 1.0171 0.078 Uiso 1 1 calc R . .
O7 O 0.6369(2) -0.29416(14) 0.7353(3) 0.0870(8) Uani 1 1 d . . .
C14 C 1.0719(2) 0.3698(2) 1.2058(3) 0.0581(7) Uani 1 1 d . . .
H14A H 1.1259 0.3315 1.2446 0.070 Uiso 1 1 calc R . .
H14B H 1.0138 0.3568 1.2405 0.070 Uiso 1 1 calc R . .
C12 C 0.6692(2) 0.31833(18) 1.1361(3) 0.0551(7) Uani 1 1 d . . .
H12 H 0.7189 0.2919 1.2007 0.066 Uiso 1 1 calc R . .
C8 C 0.6070(2) 0.36582(18) 0.9156(3) 0.0579(7) Uani 1 1 d . . .
H8 H 0.6136 0.3720 0.8290 0.069 Uiso 1 1 calc R . .
C18 C 1.1264(2) 0.3813(2) 1.0022(3) 0.0594(7) Uani 1 1 d . . .
H18A H 1.1032 0.3761 0.9062 0.071 Uiso 1 1 calc R . .
H18B H 1.1818 0.3428 1.0329 0.071 Uiso 1 1 calc R . .
C11 C 0.5846(3) 0.3496(2) 1.1696(4) 0.0669(8) Uani 1 1 d . . .
H11 H 0.5774 0.3439 1.2561 0.080 Uiso 1 1 calc R . .
C10 C 0.5118(3) 0.3886(2) 1.0763(4) 0.0722(9) Uani 1 1 d . . .
H10 H 0.4545 0.4096 1.0983 0.087 Uiso 1 1 calc R . .

C9 C 0.5232(2) 0.3968(2) 0.9500(4) 0.0736(10) Uani 1 1 d . . .
H9 H 0.4734 0.4239 0.8862 0.088 Uiso 1 1 calc R . .
C15 C 1.1060(2) 0.4561(2) 1.2431(3) 0.0718(9) Uani 1 1 d . . .
H15A H 1.1271 0.4608 1.3392 0.086 Uiso 1 1 calc R . .
H15B H 1.0498 0.4938 1.2111 0.086 Uiso 1 1 calc R . .
C17 C 1.1634(3) 0.4672(2) 1.0368(3) 0.0686(8) Uani 1 1 d . . .
H17A H 1.1106 0.5061 0.9961 0.082 Uiso 1 1 calc R . .
H17B H 1.2217 0.4778 1.0014 0.082 Uiso 1 1 calc R . .
C16 C 1.1924(3) 0.4800(2) 1.1853(4) 0.0729(9) Uani 1 1 d . . .
H16A H 1.2514 0.4468 1.2251 0.088 Uiso 1 1 calc R . .
H16B H 1.2096 0.5376 1.2051 0.088 Uiso 1 1 calc R . .

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O2 0.0453(9) 0.0335(8) 0.0485(9) -0.0041(6) 0.0188(7) -0.0065(6)
O3 0.0703(12) 0.0630(12) 0.0425(10) -0.0097(8) 0.0262(9) -0.0225(9)
O4 0.0577(11) 0.0485(10) 0.0521(10) 0.0056(8) 0.0232(8) 0.0063(8)
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C19 0.0361(11) 0.0317(11) 0.0446(11) 0.0040(9) 0.0113(9) 0.0004(8)
C24 0.0423(12) 0.0338(11) 0.0426(11) 0.0024(9) 0.0126(9) 0.0018(9)
C20 0.0393(12) 0.0391(12) 0.0456(12) -0.0011(9) 0.0136(9) -0.0004(9)
C21 0.0442(13) 0.0345(11) 0.0492(13) -0.0045(9) 0.0117(10) -0.0027(9)
C1 0.0381(11) 0.0338(11) 0.0437(11) 0.0025(9) 0.0122(9) 0.0008(9)
C2 0.0430(12) 0.0329(11) 0.0430(11) 0.0008(9) 0.0134(9) -0.0053(9)
C22 0.0410(12) 0.0367(12) 0.0523(13) 0.0039(10) 0.0116(10) -0.0041(9)
C23 0.0417(12) 0.0384(12) 0.0467(12) 0.0059(9) 0.0152(10) -0.0005(9)
N2 0.0583(13) 0.0421(12) 0.0705(15) -0.0137(10) 0.0216(12) -0.0096(10)
C13 0.0542(14) 0.0354(11) 0.0438(12) -0.0042(9) 0.0203(11) -0.0077(10)
N3 0.0511(12) 0.0535(12) 0.0471(11) -0.0077(9) 0.0218(9) -0.0107(10)
O5 0.0654(13) 0.0638(13) 0.0952(16) -0.0088(12) 0.0422(12) -0.0209(11)
C7 0.0459(13) 0.0351(11) 0.0479(13) -0.0052(9) 0.0118(10) -0.0030(9)
O6 0.1044(18) 0.0636(14) 0.0901(16) -0.0304(12) 0.0594(15) -0.0229(12)
C5 0.0483(13) 0.0372(11) 0.0377(11) -0.0025(9) 0.0115(10) -0.0025(9)
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C12 0.0618(17) 0.0540(15) 0.0550(15) 0.0037(12) 0.0247(13) 0.0044(12)
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C11 0.070(2) 0.0619(18) 0.081(2) -0.0079(15) 0.0418(17) -0.0003(15)
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C9 0.0518(17) 0.0679(19) 0.091(2) -0.0196(17) -0.0006(16) 0.0143(14)
C15 0.0597(18) 0.092(2) 0.0591(17) -0.0279(16) 0.0066(14) -0.0044(16)
C17 0.0646(19) 0.0652(19) 0.076(2) 0.0019(15) 0.0172(16) -0.0192(15)
C16 0.067(2) 0.069(2) 0.077(2) -0.0129(16) 0.0070(16) -0.0199(16)

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All esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken
into account individually in the estimation of esds in distances, angles
and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell esds is used for estimating esds involving l.s. planes.

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C14 C15 1.509(5) . ?
C12 C11 1.394(4) . ?
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C10 C9 C8 121.0(3) . . ?
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Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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O1 O 0.77921(19) 0.09903(11) 0.6499(3) 0.0342(5) Uani 1 1 d . . .

C3 C 0.7291(3) 0.16879(17) 0.6699(4) 0.0363(7) Uani 1 1 d . . .
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O3 O 0.4972(2) 0.13314(12) 0.6947(3) 0.0368(5) Uani 1 1 d . . .
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C7 C 0.3905(3) 0.14337(17) 0.4235(4) 0.0325(6) Uani 1 1 d . . .
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C13 C 0.9379(3) 0.01466(17) 0.7262(4) 0.0320(6) Uani 1 1 d . . .
C18 C 0.8905(3) -0.02515(17) 0.5948(4) 0.0320(6) Uani 1 1 d . . .
H18 H 0.8183 -0.0120 0.5220 0.038 Uiso 1 1 calc R . .
C12 C 0.3522(3) 0.10458(18) 0.2880(4) 0.0383(7) Uani 1 1 d . . .
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C11 C 0.2470(3) 0.1248(2) 0.1751(4) 0.0431(8) Uani 1 1 d . . .
H11 H 0.2230 0.0997 0.0839 0.052 Uiso 1 1 calc R . .
C6 C 0.4366(4) 0.0953(2) 0.9040(4) 0.0514(9) Uani 1 1 d . . .
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H6C H 0.5117 0.1152 0.9672 0.077 Uiso 1 1 calc R . .
O5 O 1.2664(2) -0.04709(15) 1.0262(3) 0.0469(6) Uani 1 1 d . . .
O8 O 0.8215(2) -0.10511(16) 0.3342(3) 0.0513(7) Uani 1 1 d . . .
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C16 C 1.0594(3) -0.10890(17) 0.6827(4) 0.0334(7) Uani 1 1 d . . .
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C4 0.0299(15) 0.0388(16) 0.0324(16) 0.0034(13) 0.0088(12) 0.0014(12)
O3 0.0392(12) 0.0403(12) 0.0307(11) 0.0024(9) 0.0099(9) 0.0026(10)
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C14 0.0281(15) 0.0380(16) 0.0313(15) 0.0006(12) 0.0072(12) -0.0009(12)
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O5 0.0332(12) 0.0552(15) 0.0450(14) -0.0021(12) 0.0004(10) 0.0017(11)
O8 0.0401(14) 0.0647(17) 0.0415(14) -0.0095(12) 0.0008(11) 0.0025(12)
N1 0.0359(14) 0.0425(15) 0.0345(14) -0.0037(12) 0.0119(12) -0.0064(12)
N2 0.0310(13) 0.0482(17) 0.0330(14) 0.0016(12) 0.0075(11) 0.0052(12)
C15 0.0253(14) 0.0412(17) 0.0310(15) 0.0053(13) 0.0061(12) 0.0023(12)
C17 0.0295(14) 0.0368(16) 0.0302(15) -0.0017(12) 0.0117(12) -0.0061(12)
C16 0.0305(15) 0.0361(16) 0.0352(16) 0.0030(13) 0.0124(13) -0.0003(12)
O7 0.0472(15) 0.0480(16) 0.0530(17) -0.0163(12) 0.0108(13) 0.0012(11)
O6 0.0485(14) 0.0506(15) 0.0408(14) 0.0022(12) 0.0070(11) 0.0170(12)

_geom_special_details

All esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken
into account individually in the estimation of esds in distances, angles
and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)

treatment of cell esds is used for estimating esds involving l.s. planes.

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Br1 C2 1.953(3) . ?
O1 C4 1.342(4) . ?
O1 C3 1.464(4) . ?
C3 C2 1.521(4) . ?
C2 C1 1.528(4) . ?
C4 O2 1.197(4) . ?
C4 C13 1.508(5) . ?
O3 C5 1.349(4) . ?
O3 C1 1.462(4) . ?
C7 C12 1.396(5) . ?
C7 C8 1.398(5) . ?
C7 C1 1.519(4) . ?
C8 C9 1.387(5) . ?
C5 O4 1.197(5) . ?
C5 C6 1.509(5) . ?
C9 C10 1.400(5) . ?
C14 C15 1.385(5) . ?
C14 C13 1.397(4) . ?
C10 C11 1.367(5) . ?
C13 C18 1.387(4) . ?
C18 C17 1.395(4) . ?
C12 C11 1.391(5) . ?
O5 N2 1.227(4) . ?
O8 N1 1.220(4) . ?
N1 O7 1.230(4) . ?
N1 C17 1.471(4) . ?
N2 O6 1.223(4) . ?
N2 C15 1.483(4) . ?
C15 C16 1.375(5) . ?
C17 C16 1.378(4) . ?

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C4 O1 C3 113.3(2) . . ?
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O1 C3 C2 108.2(2) . . ?
C3 C2 C1 114.9(3) . . ?
C3 C2 Br1 109.7(2) . . ?
C1 C2 Br1 108.8(2) . . ?
O2 C4 O1 124.9(3) . . ?
O2 C4 C13 123.6(3) . . ?
O1 C4 C13 111.5(3) . . ?
C5 O3 C1 116.9(3) . . ?
C12 C7 C8 119.3(3) . . ?

C12 C7 C1 120.1(3) . . ?
C8 C7 C1 120.5(3) . . ?
C9 C8 C7 120.4(3) . . ?
O3 C1 C7 109.7(3) . . ?
O3 C1 C2 103.0(2) . . ?
C7 C1 C2 111.9(3) . . ?
O4 C5 O3 123.4(4) . . ?
O4 C5 C6 126.2(4) . . ?
O3 C5 C6 110.3(3) . . ?
C8 C9 C10 119.7(3) . . ?
C15 C14 C13 118.5(3) . . ?
C11 C10 C9 120.0(3) . . ?
C18 C13 C14 120.8(3) . . ?
C18 C13 C4 124.0(3) . . ?
C14 C13 C4 115.2(3) . . ?
C13 C18 C17 117.7(3) . . ?
C11 C12 C7 119.7(3) . . ?
C10 C11 C12 121.0(3) . . ?
O8 N1 O7 124.0(3) . . ?
O8 N1 C17 118.7(3) . . ?
O7 N1 C17 117.2(3) . . ?
O6 N2 O5 124.8(3) . . ?
O6 N2 C15 117.8(3) . . ?
O5 N2 C15 117.4(3) . . ?
C16 C15 C14 122.8(3) . . ?
C16 C15 N2 118.6(3) . . ?
C14 C15 N2 118.6(3) . . ?
C16 C17 C18 123.3(3) . . ?
C16 C17 N1 117.7(3) . . ?
C18 C17 N1 119.0(3) . . ?
C15 C16 C17 116.9(3) . . ?

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Crystallographic Information File for 51c (Chapter IV)

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'H' 'H' 0.0000 0.0000
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_symmetry_space_group_name_H-M	P2(1)/c

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'x, -y-1/2, z-1/2'

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_computing_data_reduction	'CrystalClear (Rigaku/MSC, 2006)'
_computing_structure_solution	'SHELXS-97 (Sheldrick, 1990)'
_computing_structure_refinement	'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics	'DIAMOND (Bradenburg, 1999)'

_computing_publication_material 'SHELXL-97 (Sheldrick, 1997)'

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_refine_ls_number_reflns 3789
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_refine_ls_number_restraints 0
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_atom_site_occupancy
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N1 N 0.6656(3) 0.8180(5) 0.12447(8) 0.0418(7) Uani 1 1 d . . .
O2 O 0.7287(3) 0.5527(4) 0.08460(8) 0.0552(7) Uani 1 1 d . . .
C6 C 0.7037(3) 0.9601(6) 0.15629(10) 0.0438(8) Uani 1 1 d . . .
H6 H 0.8006 0.9950 0.1543 0.053 Uiso 1 1 calc R . .
C1 C 0.7556(4) 0.6734(6) 0.11104(10) 0.0441(8) Uani 1 1 d . . .
C12 C 0.6055(4) 0.6775(6) 0.19926(11) 0.0496(9) Uani 1 1 d . . .
H12 H 0.5505 0.6272 0.1788 0.059 Uiso 1 1 calc R . .
C19 C 0.4129(3) 0.9333(6) 0.04101(10) 0.0465(8) Uani 1 1 d . . .
C18 C 0.5404(4) 0.9548(7) 0.06668(11) 0.0501(9) Uani 1 1 d . . .
H18A H 0.5574 1.1076 0.0720 0.060 Uiso 1 1 calc R . .
H18B H 0.6177 0.8983 0.0539 0.060 Uiso 1 1 calc R . .
C7 C 0.6932(3) 0.8530(6) 0.19421(10) 0.0453(8) Uani 1 1 d . . .
C2 C 1.0004(4) 0.5788(7) 0.11728(12) 0.0537(10) Uani 1 1 d . . .
C8 C 0.7761(4) 0.9279(7) 0.22530(12) 0.0601(11) Uani 1 1 d . . .
C10 C 0.6800(5) 0.6448(9) 0.26381(13) 0.0719(13) Uani 1 1 d . . .
H10 H 0.6779 0.5743 0.2869 0.086 Uiso 1 1 calc R . .
C24 C 0.3863(4) 0.7425(7) 0.02152(11) 0.0559(10) Uani 1 1 d . . .
H24 H 0.4469 0.6266 0.0247 0.067 Uiso 1 1 calc R . .
C20 C 0.3191(4) 1.1042(7) 0.03625(12) 0.0590(10) Uani 1 1 d . . .
H20 H 0.3347 1.2342 0.0492 0.071 Uiso 1 1 calc R . .
C11 C 0.5984(5) 0.5762(7) 0.23401(13) 0.0642(11) Uani 1 1 d . . .
H11 H 0.5378 0.4617 0.2368 0.077 Uiso 1 1 calc R . .
C23 C 0.2719(5) 0.7203(9) -0.00253(13) 0.0703(13) Uani 1 1 d . . .
H23 H 0.2558 0.5910 -0.0157 0.084 Uiso 1 1 calc R . .
C5 C 1.0282(5) 0.6714(9) 0.07975(15) 0.0781(14) Uani 1 1 d . . .
H5A H 1.0364 0.8268 0.0817 0.117 Uiso 1 1 calc R . .
H5B H 0.9542 0.6354 0.0619 0.117 Uiso 1 1 calc R . .
H5C H 1.1118 0.6116 0.0715 0.117 Uiso 1 1 calc R . .
C21 C 0.2035(4) 1.0808(10) 0.01238(14) 0.0743(14) Uani 1 1 d . . .
H21 H 0.1408 1.1941 0.0095 0.089 Uiso 1 1 calc R . .
C9 C 0.7661(5) 0.8191(9) 0.25975(14) 0.0759(14) Uani 1 1 d . . .
H9 H 0.8197 0.8667 0.2806 0.091 Uiso 1 1 calc R . .
C4 C 0.9852(5) 0.3346(7) 0.1170(2) 0.0854(17) Uani 1 1 d . . .
H4A H 0.9678 0.2851 0.1419 0.128 Uiso 1 1 calc R . .
H4B H 1.0680 0.2692 0.1093 0.128 Uiso 1 1 calc R . .
H4C H 0.9103 0.2940 0.0998 0.128 Uiso 1 1 calc R . .
C3 C 1.1066(4) 0.6521(9) 0.14698(15) 0.0743(14) Uani 1 1 d . . .
H3A H 1.0873 0.5893 0.1708 0.111 Uiso 1 1 calc R . .
H3B H 1.1050 0.8079 0.1489 0.111 Uiso 1 1 calc R . .
H3C H 1.1954 0.6057 0.1402 0.111 Uiso 1 1 calc R . .
C22 C 0.1815(5) 0.8909(11) -0.00698(13) 0.0771(15) Uani 1 1 d . . .
H22 H 0.1043 0.8767 -0.0234 0.092 Uiso 1 1 calc R . .
C13 C 0.8776(5) 1.1088(9) 0.22206(15) 0.0820(15) Uani 1 1 d . . .
H13A H 0.8713 1.1652 0.1968 0.123 Uiso 1 1 calc R . .
H13B H 0.9683 1.0542 0.2279 0.123 Uiso 1 1 calc R . .
H13C H 0.8583 1.2229 0.2394 0.123 Uiso 1 1 calc R . .
C17 C 0.5292(3) 0.8327(6) 0.10388(10) 0.0426(8) Uani 1 1 d . . .

H17 H 0.4970 0.6847 0.0982 0.051 Uiso 1 1 calc R . .
C15 C 0.4759(4) 1.1596(6) 0.14198(11) 0.0523(9) Uani 1 1 d . . .
C16 C 0.4265(3) 0.9430(6) 0.12820(10) 0.0483(9) Uani 1 1 d . . .
H16A H 0.3403 0.9608 0.1136 0.058 Uiso 1 1 calc R . .
H16B H 0.4104 0.8506 0.1496 0.058 Uiso 1 1 calc R . .
C14 C 0.6258(4) 1.1785(6) 0.15221(12) 0.0517(9) Uani 1 1 d . . .
H14A H 0.6381 1.2571 0.1758 0.062 Uiso 1 1 calc R . .
H14B H 0.6670 1.2649 0.1331 0.062 Uiso 1 1 calc R . .
O3 O 0.4014(3) 1.3176(5) 0.14422(10) 0.0736(9) Uani 1 1 d . . .

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N1 0.0343(14) 0.0440(15) 0.0474(17) -0.0010(12) 0.0035(12) 0.0039(12)
O2 0.0553(15) 0.0571(16) 0.0541(16) -0.0064(13) 0.0089(12) 0.0062(12)
C6 0.0350(16) 0.0438(18) 0.053(2) -0.0025(15) 0.0019(14) -0.0019(14)
C1 0.0437(18) 0.0443(18) 0.045(2) 0.0029(16) 0.0070(15) -0.0010(15)
C12 0.049(2) 0.0462(19) 0.054(2) -0.0047(16) 0.0076(16) 0.0051(16)
C19 0.0418(18) 0.059(2) 0.0387(18) 0.0090(16) 0.0062(14) -0.0001(16)
C18 0.0423(18) 0.056(2) 0.053(2) 0.0046(17) 0.0062(15) 0.0006(16)
C7 0.0375(18) 0.0508(19) 0.048(2) -0.0037(16) 0.0026(14) 0.0061(15)
C2 0.0370(18) 0.059(2) 0.067(3) 0.0109(19) 0.0176(17) 0.0116(16)
C8 0.049(2) 0.071(3) 0.059(3) -0.011(2) -0.0013(18) 0.0011(19)
C10 0.080(3) 0.087(3) 0.049(2) 0.012(2) 0.013(2) 0.017(3)
C24 0.055(2) 0.063(2) 0.051(2) 0.0020(18) 0.0093(17) -0.0012(19)
C20 0.054(2) 0.067(2) 0.056(2) 0.010(2) 0.0044(18) 0.0102(19)
C11 0.070(3) 0.062(2) 0.063(3) 0.009(2) 0.020(2) 0.009(2)
C23 0.066(3) 0.091(3) 0.054(3) -0.004(2) 0.009(2) -0.021(3)
C5 0.062(3) 0.099(4) 0.076(3) 0.016(3) 0.030(2) 0.002(2)
C21 0.045(2) 0.102(4) 0.076(3) 0.030(3) 0.007(2) 0.014(2)
C9 0.074(3) 0.099(4) 0.054(3) -0.017(3) -0.006(2) 0.015(3)
C4 0.059(3) 0.058(3) 0.141(5) 0.013(3) 0.022(3) 0.012(2)
C3 0.044(2) 0.088(3) 0.090(4) 0.014(3) 0.001(2) 0.012(2)
C22 0.050(2) 0.132(5) 0.049(2) 0.021(3) -0.0029(18) -0.017(3)
C13 0.063(3) 0.097(4) 0.083(4) -0.019(3) -0.016(2) -0.020(3)
C17 0.0335(16) 0.0471(18) 0.047(2) 0.0018(15) 0.0005(14) -0.0023(14)
C15 0.048(2) 0.056(2) 0.053(2) 0.0002(17) 0.0093(16) 0.0093(17)
C16 0.0363(17) 0.062(2) 0.047(2) 0.0072(17) 0.0068(14) 0.0018(16)
C14 0.052(2) 0.0413(18) 0.062(2) -0.0011(16) 0.0042(17) 0.0014(16)
O3 0.0656(18) 0.0689(19) 0.086(2) -0.0100(16) 0.0024(16) 0.0269(16)

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 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix. The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry. An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.

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O1 C2 1.480(4) . ?
N1 C1 1.359(4) . ?
N1 C6 1.459(4) . ?
N1 C17 1.486(4) . ?
O2 C1 1.213(4) . ?
C6 C7 1.509(5) . ?
C6 C14 1.545(5) . ?
C12 C11 1.389(6) . ?
C12 C7 1.397(5) . ?
C19 C24 1.378(6) . ?
C19 C20 1.398(5) . ?
C19 C18 1.507(5) . ?
C18 C17 1.530(5) . ?
C7 C8 1.409(5) . ?
C2 C5 1.491(6) . ?
C2 C3 1.505(6) . ?
C2 C4 1.508(6) . ?
C8 C9 1.404(7) . ?
C8 C13 1.501(6) . ?
C10 C11 1.355(7) . ?
C10 C9 1.376(7) . ?
C24 C23 1.374(6) . ?
C20 C21 1.381(6) . ?
C23 C22 1.375(8) . ?
C21 C22 1.365(8) . ?
C17 C16 1.525(5) . ?
C15 O3 1.220(4) . ?
C15 C16 1.488(5) . ?
C15 C14 1.496(5) . ?

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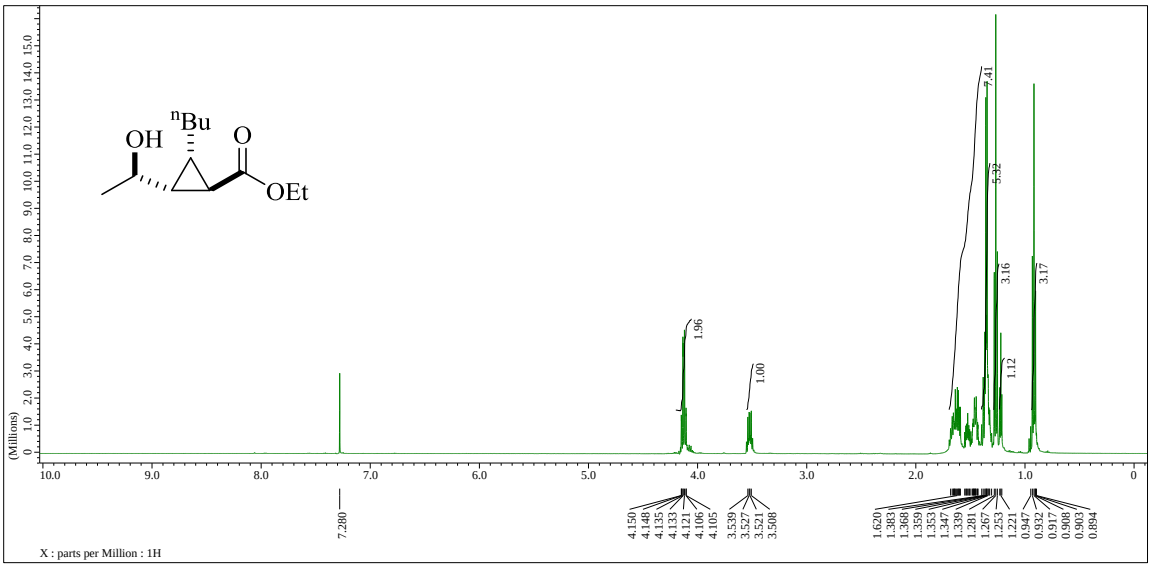
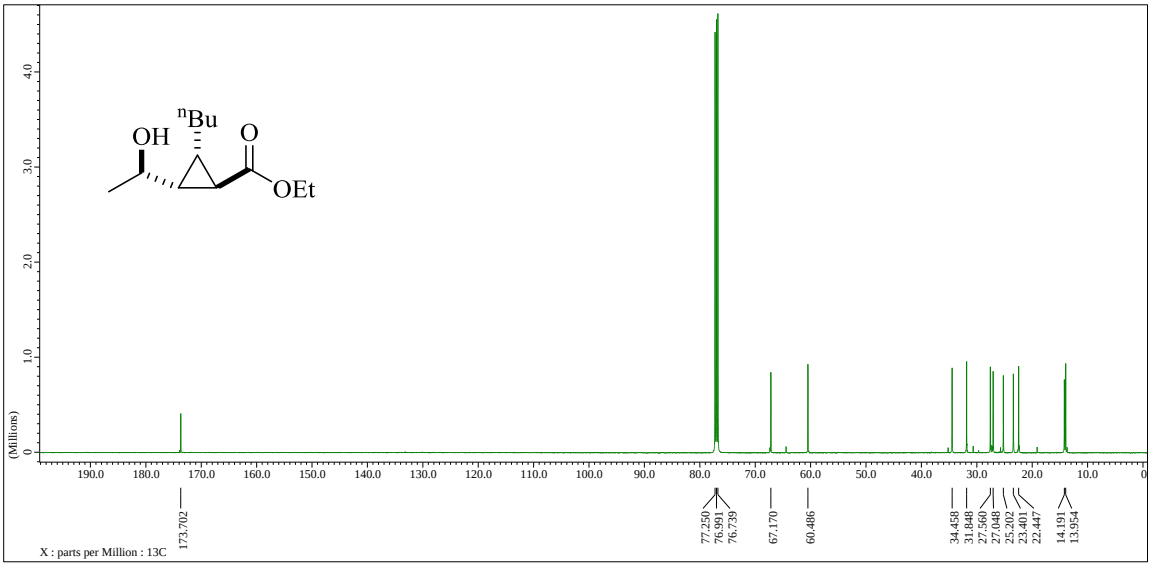
C1 N1 C6 121.5(3) . . ?
C1 N1 C17 116.7(3) . . ?
C6 N1 C17 121.6(3) . . ?
N1 C6 C7 113.8(3) . . ?
N1 C6 C14 110.2(3) . . ?
C7 C6 C14 113.7(3) . . ?
O2 C1 O1 125.1(3) . . ?
O2 C1 N1 123.8(3) . . ?
O1 C1 N1 111.0(3) . . ?
C11 C12 C7 121.7(4) . . ?
C24 C19 C20 118.4(4) . . ?
C24 C19 C18 120.2(3) . . ?
C20 C19 C18 121.4(4) . . ?
C19 C18 C17 112.4(3) . . ?
C12 C7 C8 118.7(4) . . ?
C12 C7 C6 121.8(3) . . ?
C8 C7 C6 119.4(3) . . ?
O1 C2 C5 109.0(3) . . ?
O1 C2 C3 101.0(3) . . ?
C5 C2 C3 110.9(4) . . ?
O1 C2 C4 110.4(3) . . ?
C5 C2 C4 113.4(5) . . ?
C3 C2 C4 111.4(4) . . ?
C9 C8 C7 117.5(4) . . ?
C9 C8 C13 120.1(4) . . ?
C7 C8 C13 122.3(4) . . ?
C11 C10 C9 119.7(4) . . ?
C23 C24 C19 121.3(4) . . ?
C21 C20 C19 120.3(4) . . ?
C10 C11 C12 119.8(4) . . ?
C24 C23 C22 119.4(5) . . ?
C22 C21 C20 119.8(4) . . ?
C10 C9 C8 122.5(4) . . ?
C21 C22 C23 120.8(4) . . ?
N1 C17 C16 110.6(3) . . ?
N1 C17 C18 110.2(3) . . ?
C16 C17 C18 110.9(3) . . ?
O3 C15 C16 123.3(4) . . ?
O3 C15 C14 120.3(4) . . ?
C16 C15 C14 116.3(3) . . ?
C15 C16 C17 111.8(3) . . ?

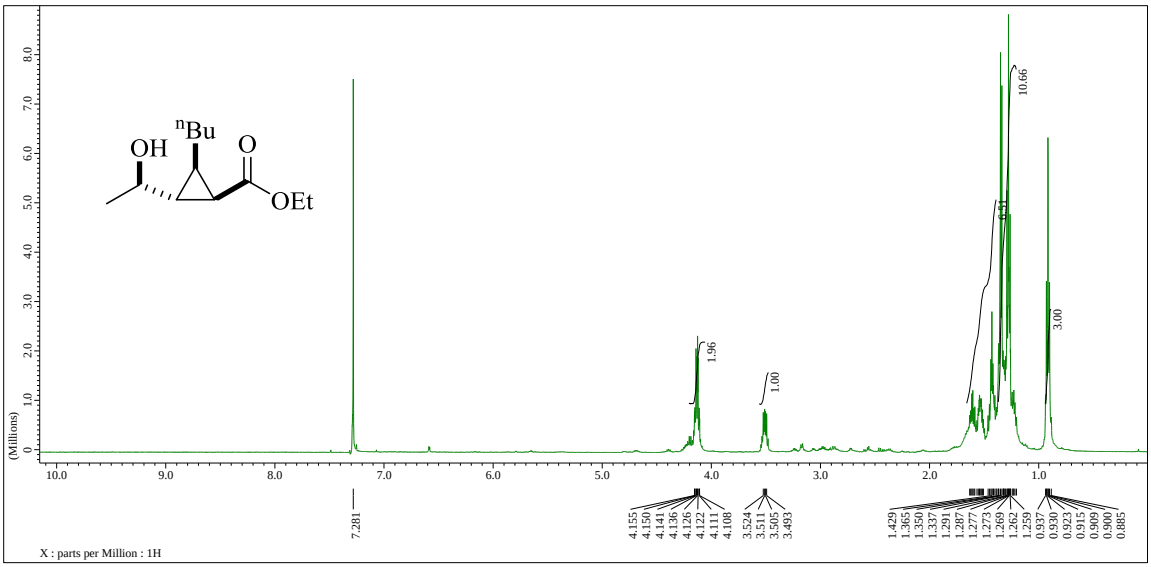
C15 C14 C6 115.3(3) . . ?

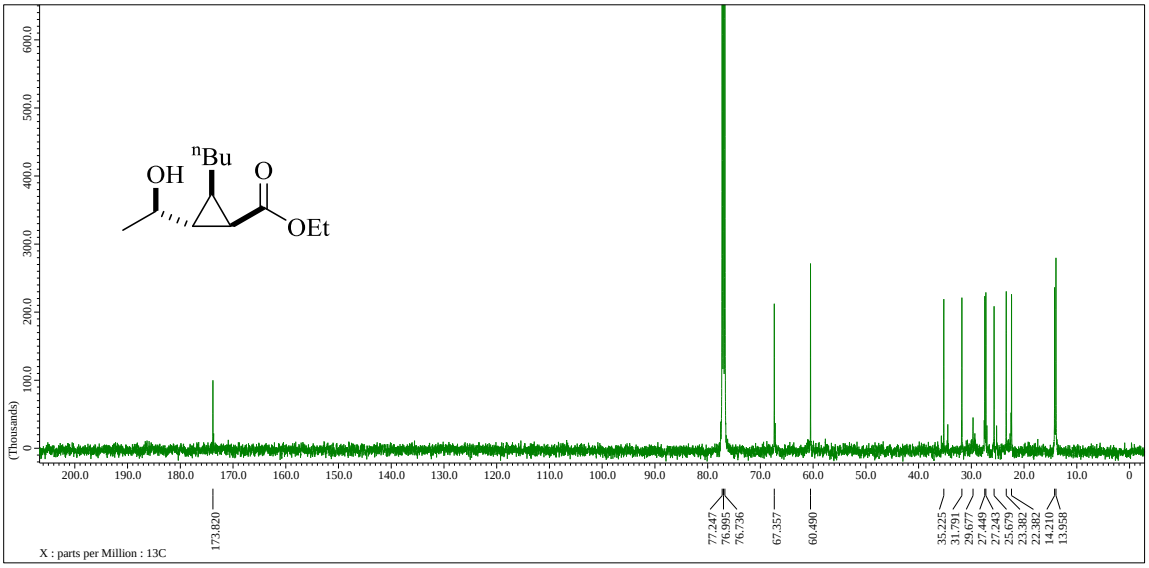
_diffrn_measured_fraction_theta_max	0.998
_diffrn_reflns_theta_full	25.05
_diffrn_measured_fraction_theta_full	0.998
_refine_diff_density_max	0.437
_refine_diff_density_min	-0.318
_refine_diff_density_rms	0.066

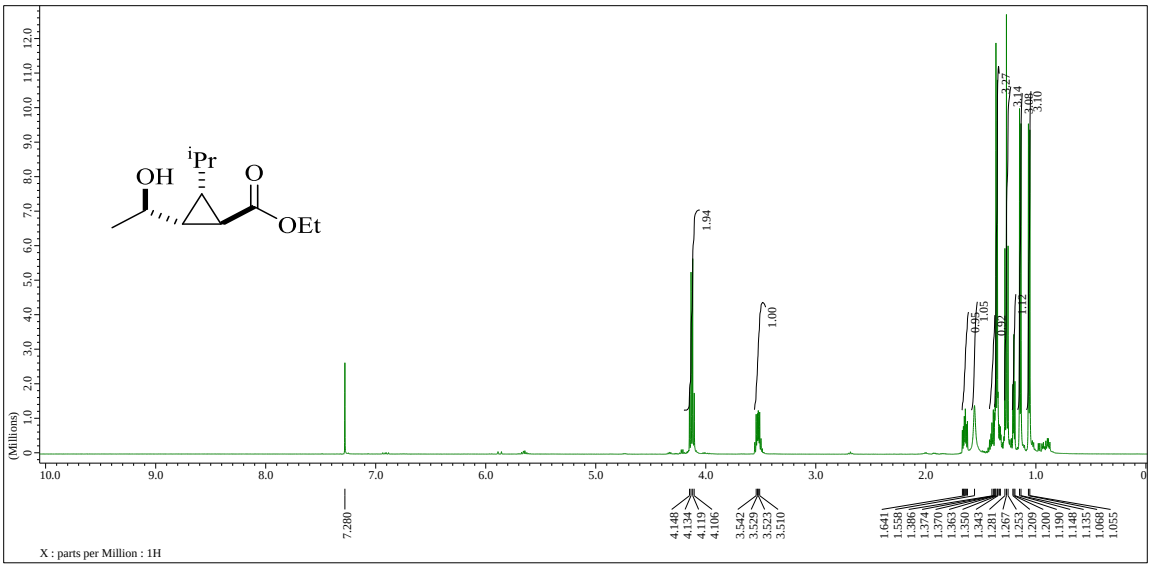
Appendix B: NMR Spectra

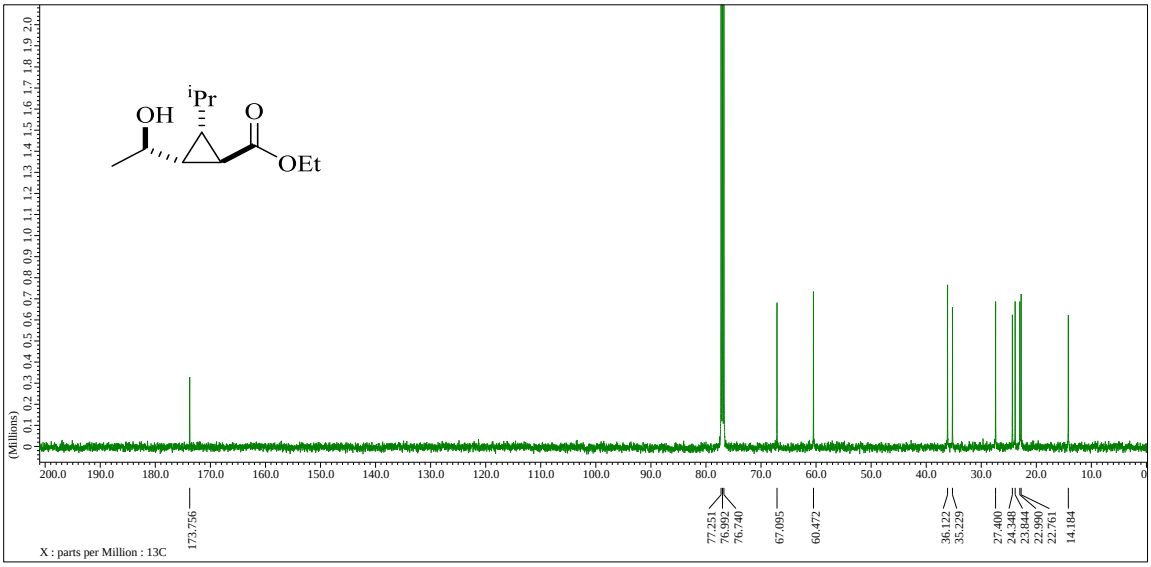

OH
nBu
O
OEt
(Millions)
7.41
5.32
3.16
3.17
1.96
1.00
1.12
7.280
4.150
4.148
4.135
4.133
4.121
4.106
4.105
3.539
3.527
3.521
3.508
1.620
1.383
1.368
1.359
1.353
1.347
1.339
1.281
1.267
1.253
1.221
0.947
0.932
0.917
0.908
0.903
0.894
X : parts per Million : 1H

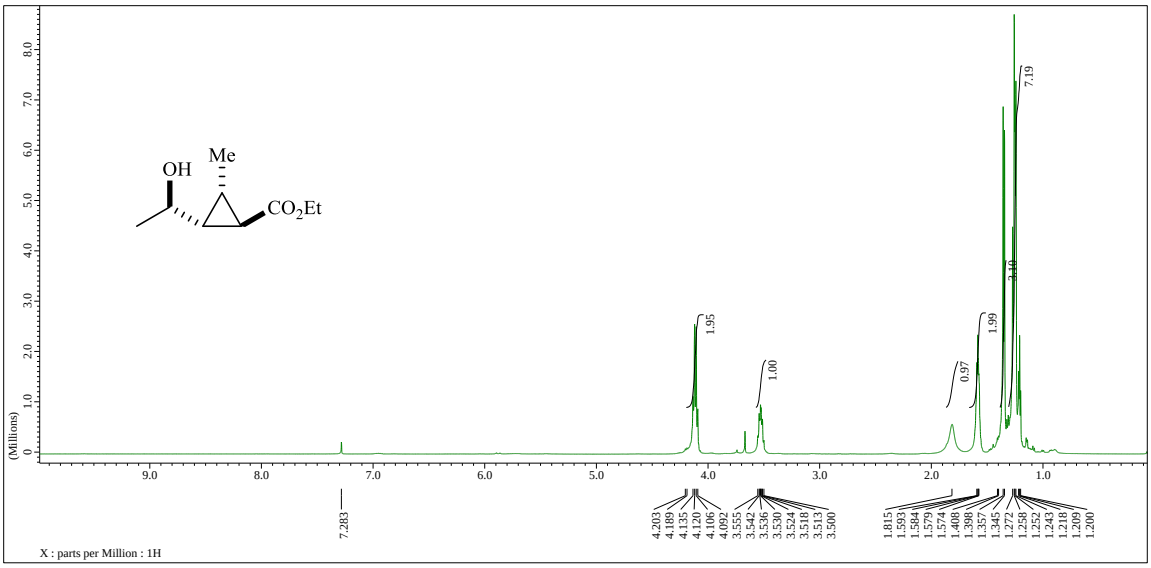

OH
nBu
O
OEt
(Millions)
173.702
77.250
76.991
76.739
67.170
60.486
34.458
31.848
27.560
27.048
25.202
23.401
22.447
14.191
13.954
X : parts per Million : 13C

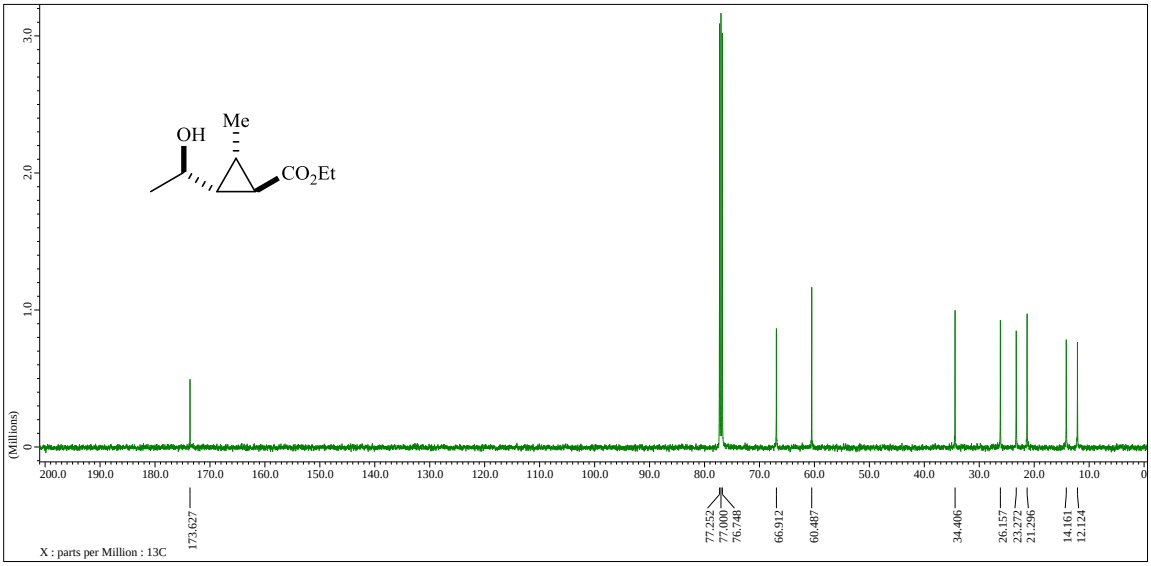

OH
nBu
O
OEt
(Millions)
X : parts per Million : 1H
7.281
4.155
4.150
4.141
4.136
4.126
4.122
4.111
4.108
3.524
3.511
3.505
3.493
1.429
1.365
1.350
1.337
1.291
1.287
1.277
1.273
1.269
1.262
1.259
0.937
0.930
0.923
0.915
0.909
0.900
0.885
1.96
1.00
10.66
6.51
3.00

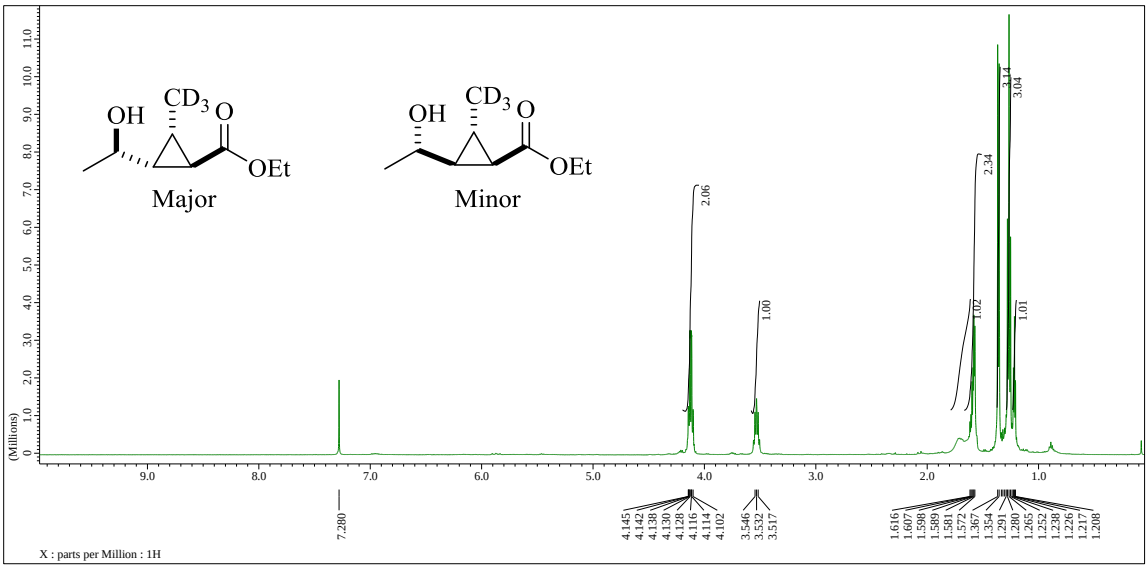

OH
nBu
O
OEt
(Thousands)
X : parts per Million : 13C
173.820
77.247
76.995
76.736
67.357
60.490
35.225
31.791
29.677
27.449
27.243
25.679
23.382
22.316
14.210
13.958

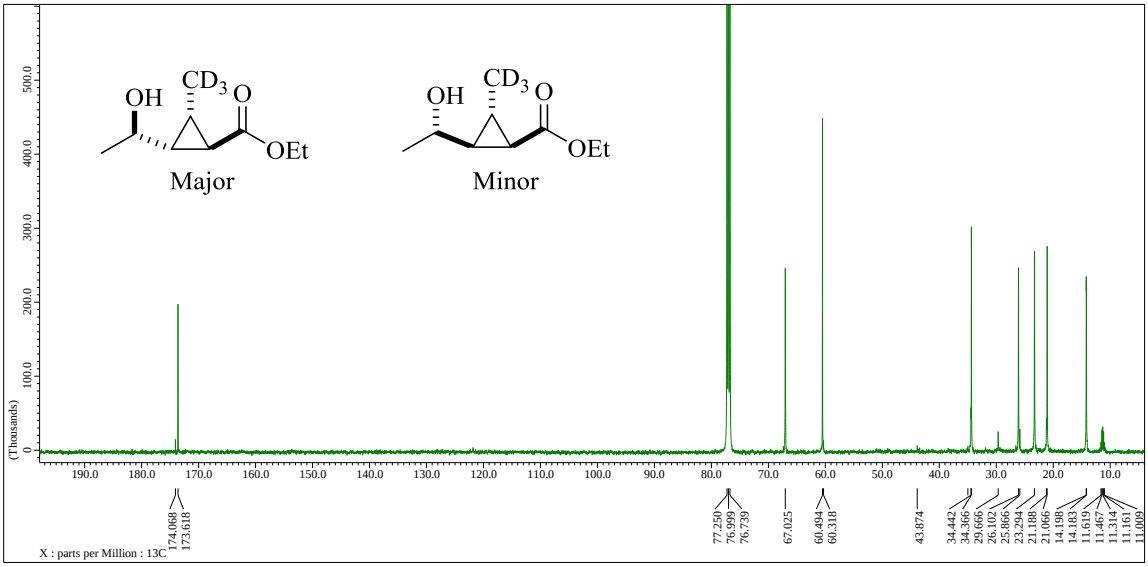

OH
iPr
O
OEt
1.94
1.00
0.96
1.05
0.97
1.12
3.27
3.14
3.08
3.10
(Millions)
7.280
4.148
4.134
4.119
4.106
3.542
3.529
3.523
3.510
1.641
1.558
1.386
1.374
1.370
1.363
1.350
1.343
1.281
1.267
1.253
1.209
1.200
1.190
1.148
1.135
1.068
1.055
X : parts per Million : 1H

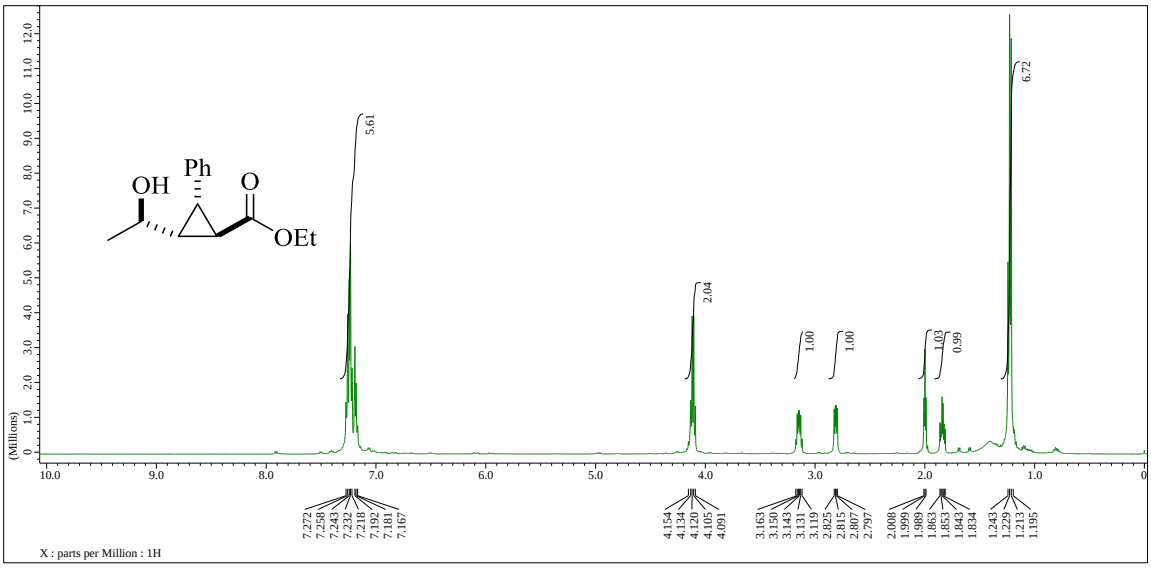

OH
iPr
O
OEt
(Millions)
173.756
77.251
76.992
76.740
67.095
60.472
36.122
35.229
27.400
24.348
23.844
22.990
22.761
14.184
X : parts per Million : 13C

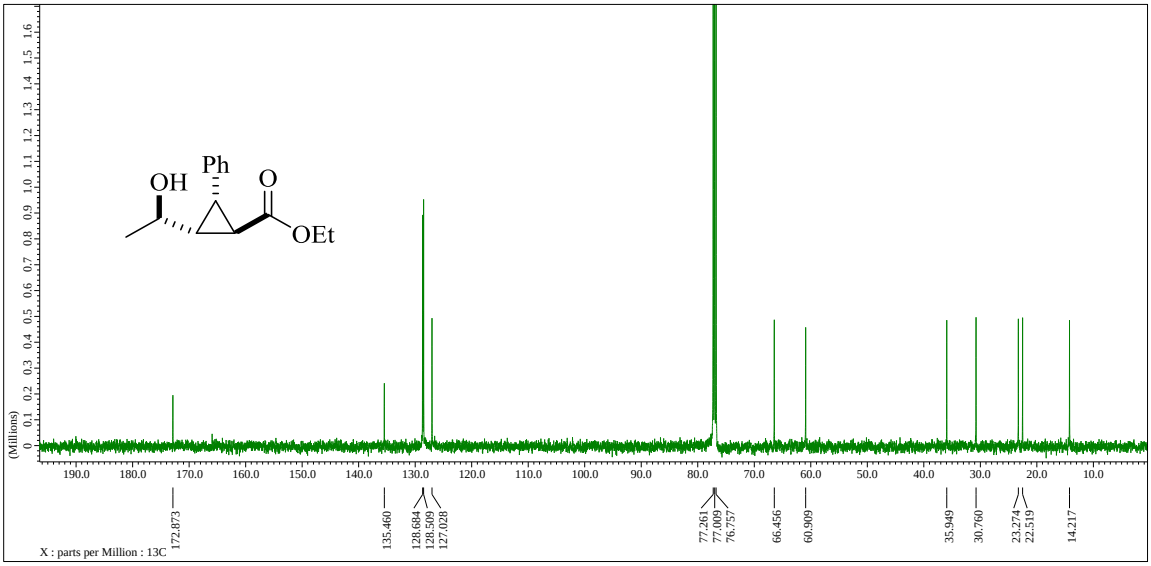

OH
Me
CO2Et
(Millions)
X : parts per Million : 1H

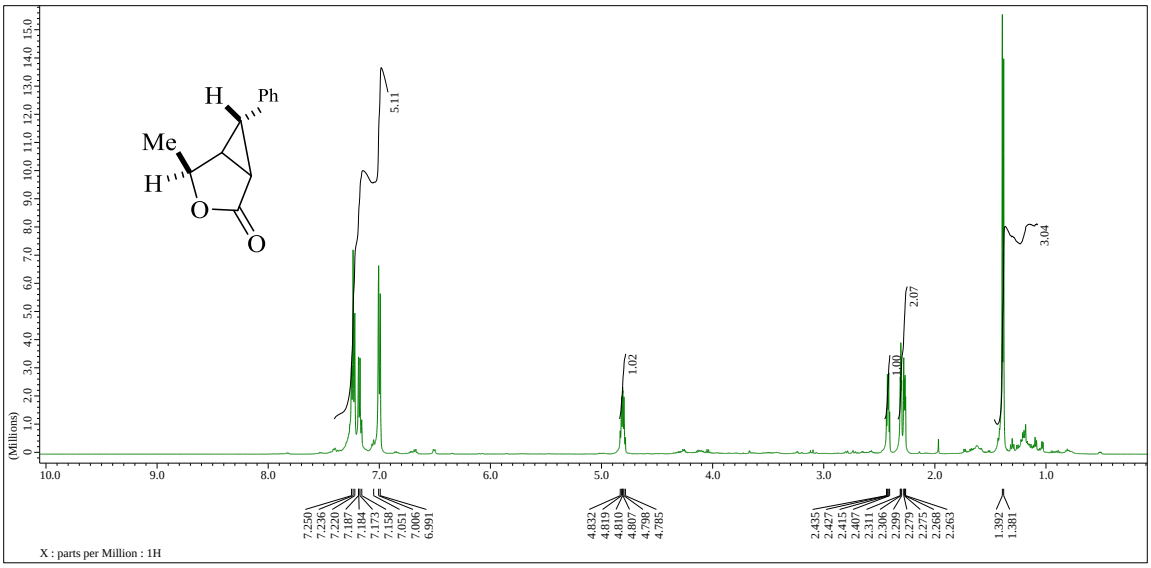

OH
Me
CO2Et
(Millions)
X : parts per Million : 13C

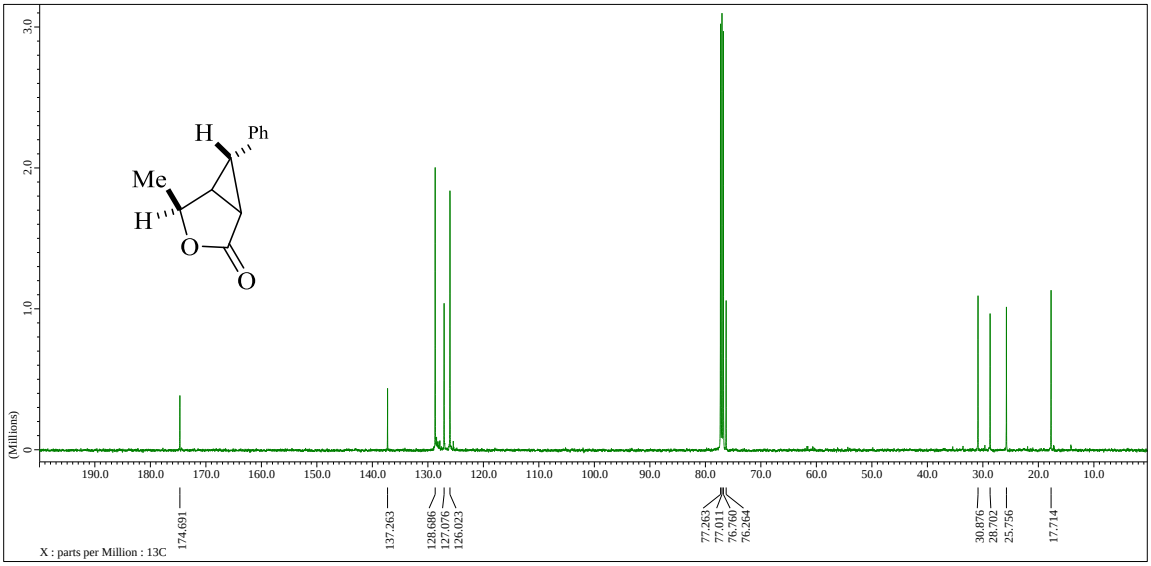

OH
CD3
O
OEt
Major
OH
CD3
O
OEt
Minor
(Millions)
2.06
1.00
2.34
1.02
3.14
3.04
1.01
7.280
4.145
4.142
4.138
4.130
4.128
4.116
4.114
4.102
3.546
3.532
3.517
1.616
1.607
1.598
1.589
1.581
1.572
1.367
1.354
1.291
1.280
1.265
1.252
1.238
1.226
1.217
1.208
X : parts per Million : 1H

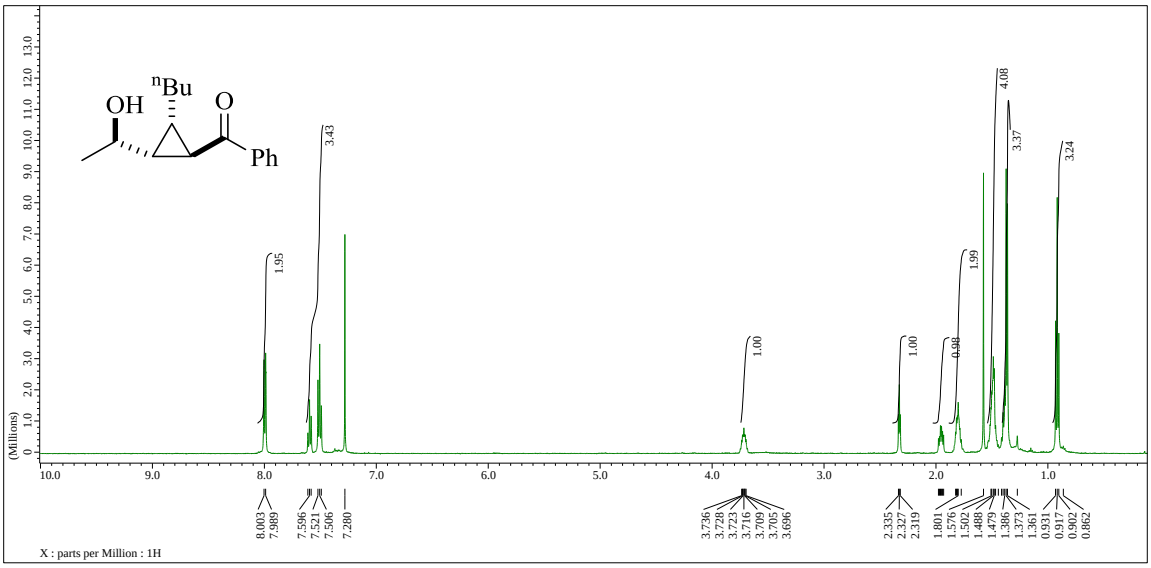

OH
CD3
O
OEt
Major
OH
CD3
O
OEt
Minor
(Thousands)
174.068
173.618
77.250
76.999
76.739
67.025
60.494
60.318
43.874
34.442
34.366
29.666
26.102
25.866
23.294
21.188
21.066
14.198
14.183
11.619
11.467
11.314
11.161
11.009
X : parts per Million : 13C

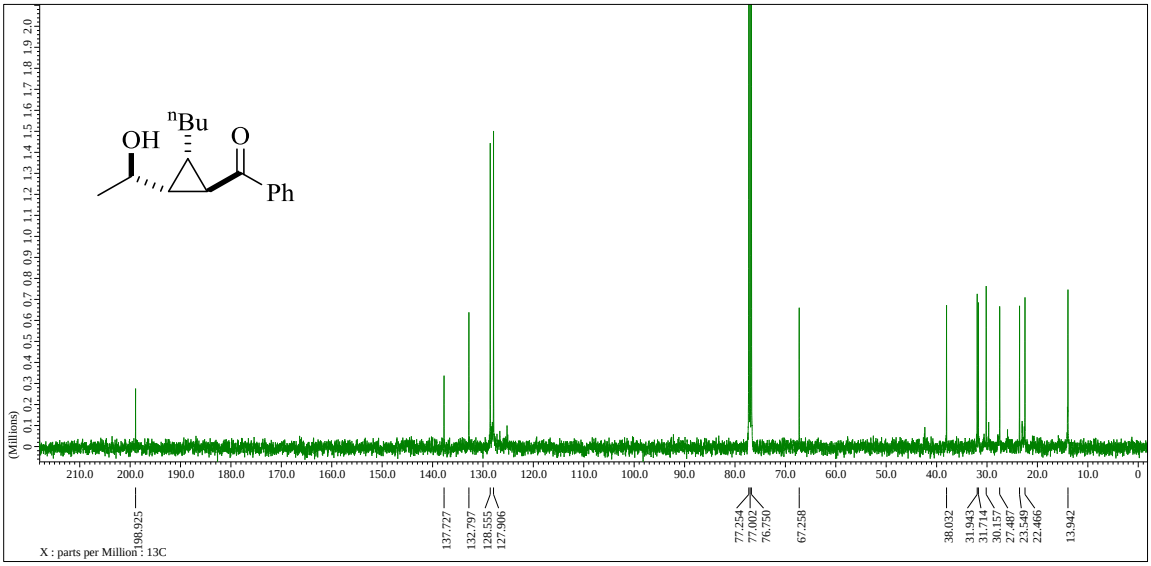

OH
Ph
O
OEt
5.61
2.04
1.00
1.00
1.03
0.99
6.72
(Millions)
X : parts per Million : 1H

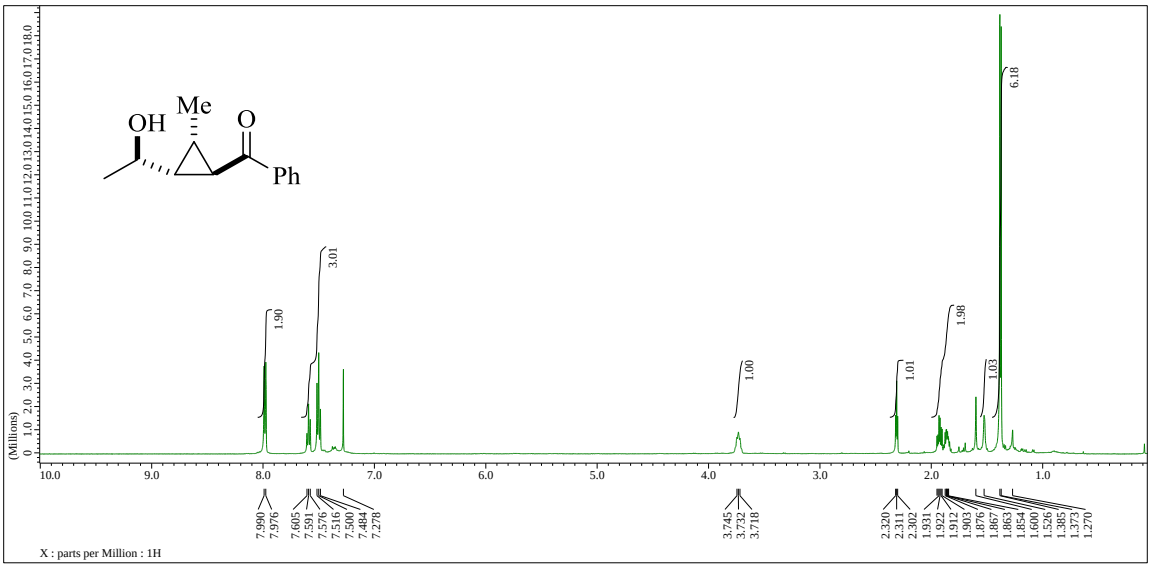

OH
Ph
O
OEt
(Millions)
172.873
135.460
128.684
128.509
127.028
77.261
77.009
76.757
66.456
60.909
35.949
30.760
23.274
22.519
14.217
X : parts per Million : 13C

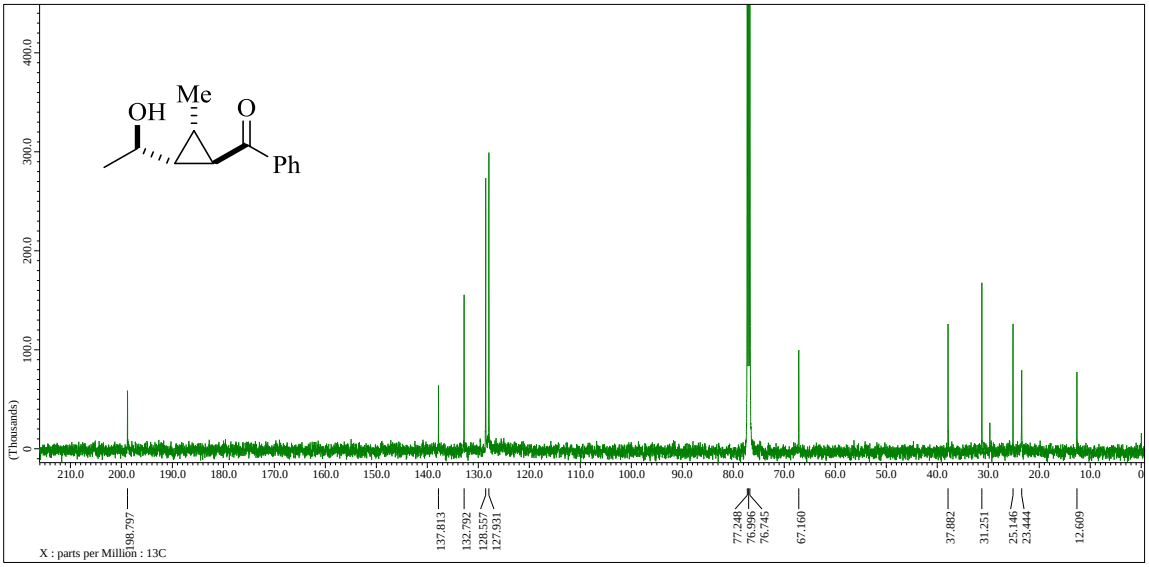

H
Ph
Me
H
O
O
5.11
1.02
1.00
2.07
3.04
(Millions)
X : parts per Million : 1H

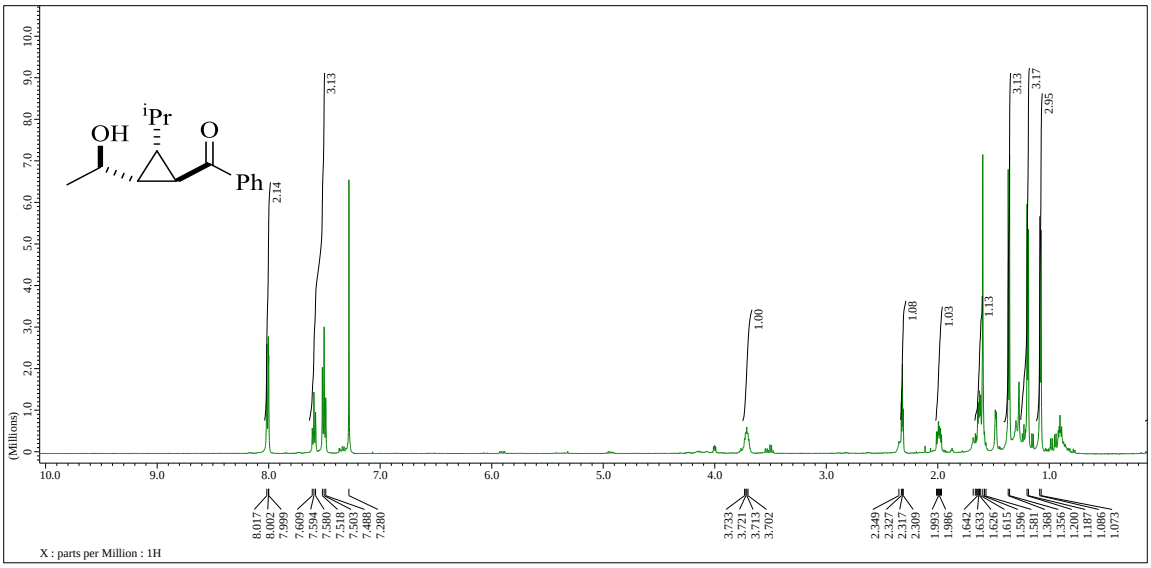

H
Ph
Me
H
O
O
(Millions)
174.691
137.263
128.686
127.076
126.023
77.263
77.011
76.760
76.264
30.976
28.702
25.756
17.714
X : parts per Million : 13C

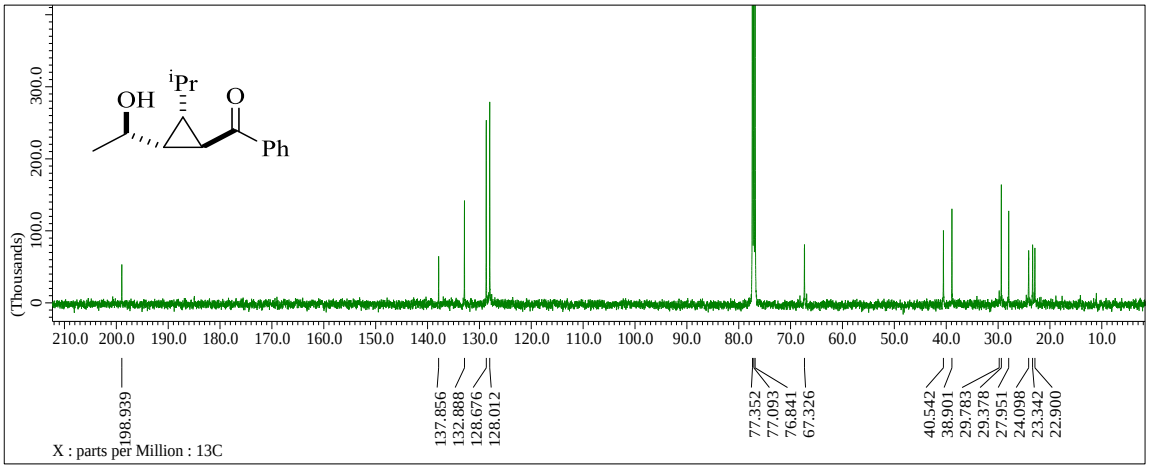

OH
nBu
O
Ph
(Millions)
X : parts per Million : 1H

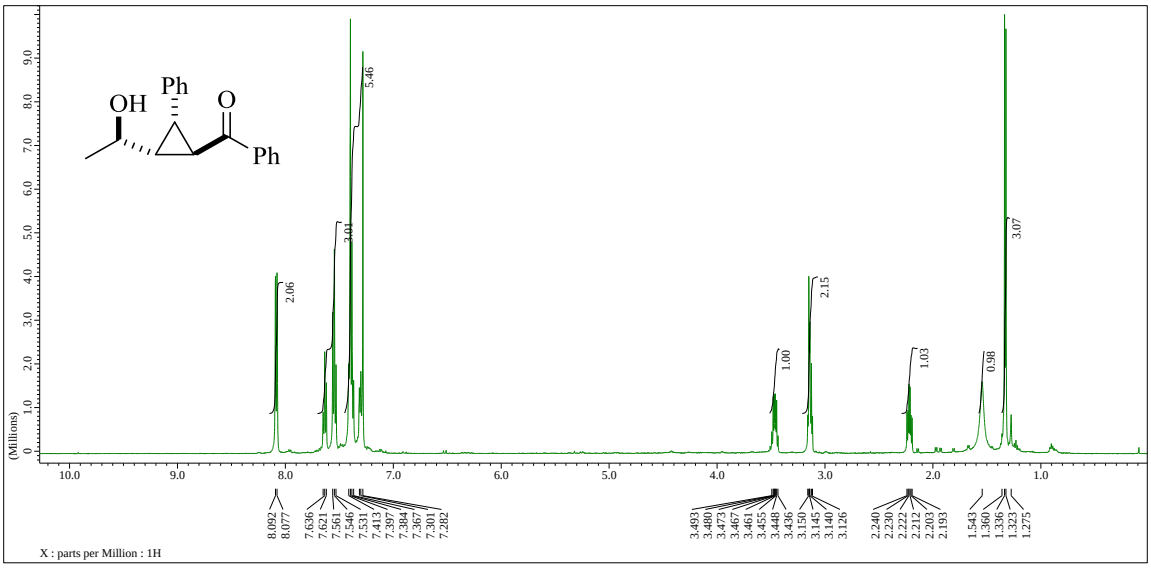

OH
nBu
O
Ph
(Millions)
X : parts per Million : 13C

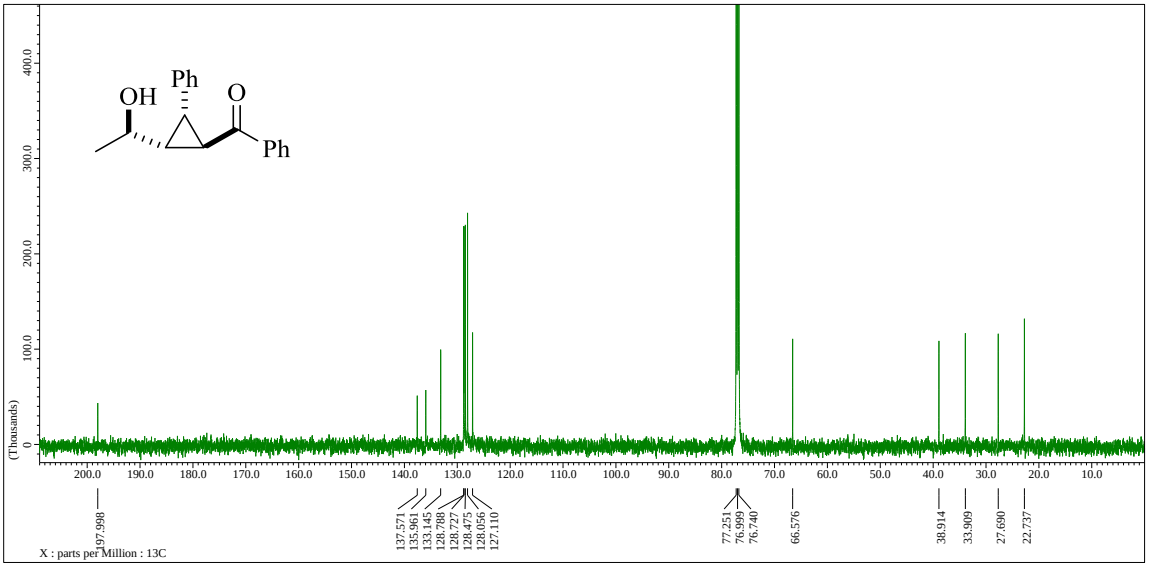

OH
Me
O
Ph
(Millions)
1.90
3.01
1.00
1.01
1.98
1.03
6.18
7.990
7.976
7.605
7.591
7.576
7.516
7.500
7.484
7.278
3.745
3.732
3.718
2.320
2.311
2.302
1.931
1.922
1.912
1.903
1.676
1.667
1.863
1.854
1.600
1.526
1.385
1.373
1.270
X : parts per Million : 1H

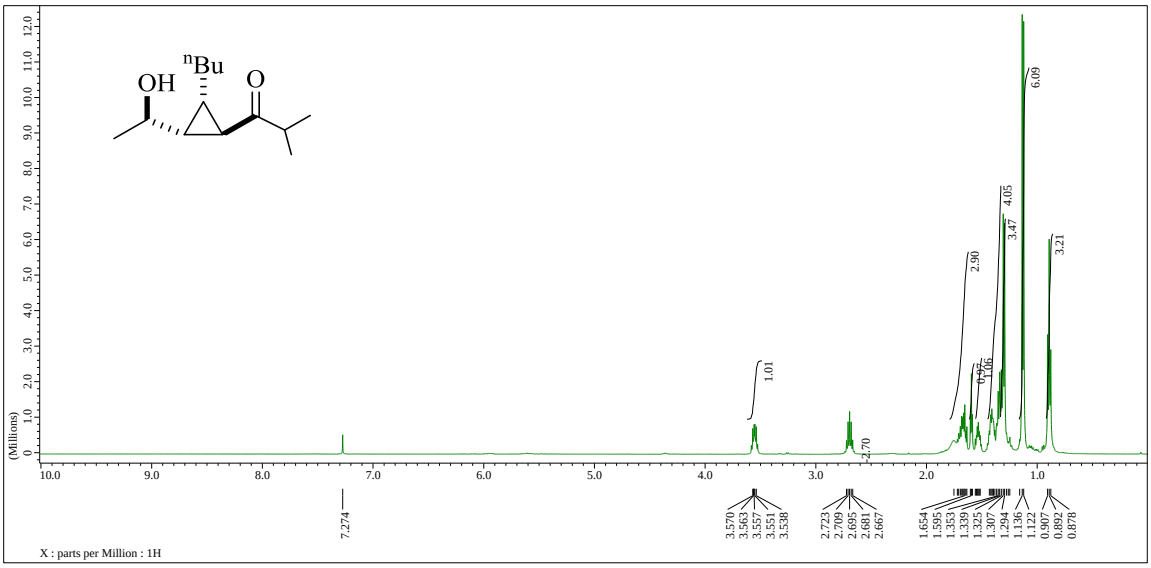

OH
Me
O
Ph
(Thousands)
198.797
137.813
132.792
128.557
127.931
77.248
76.996
76.745
67.160
37.882
31.251
25.146
23.444
12.609
X : parts per Million : 13C

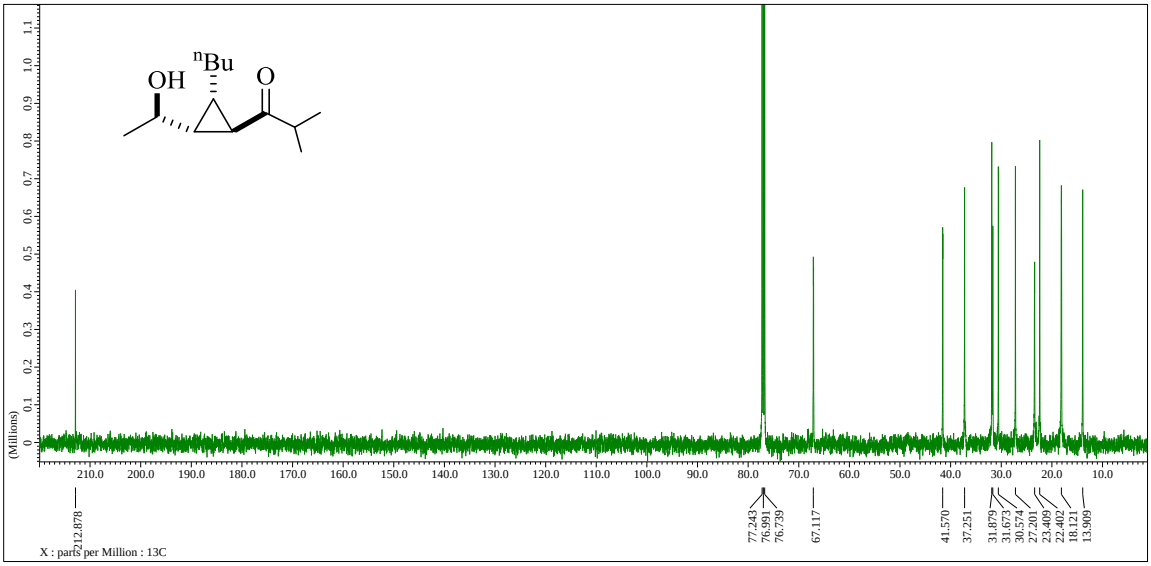

OH
iPr
O
Ph
(Millions)
X : parts per Million : 1H

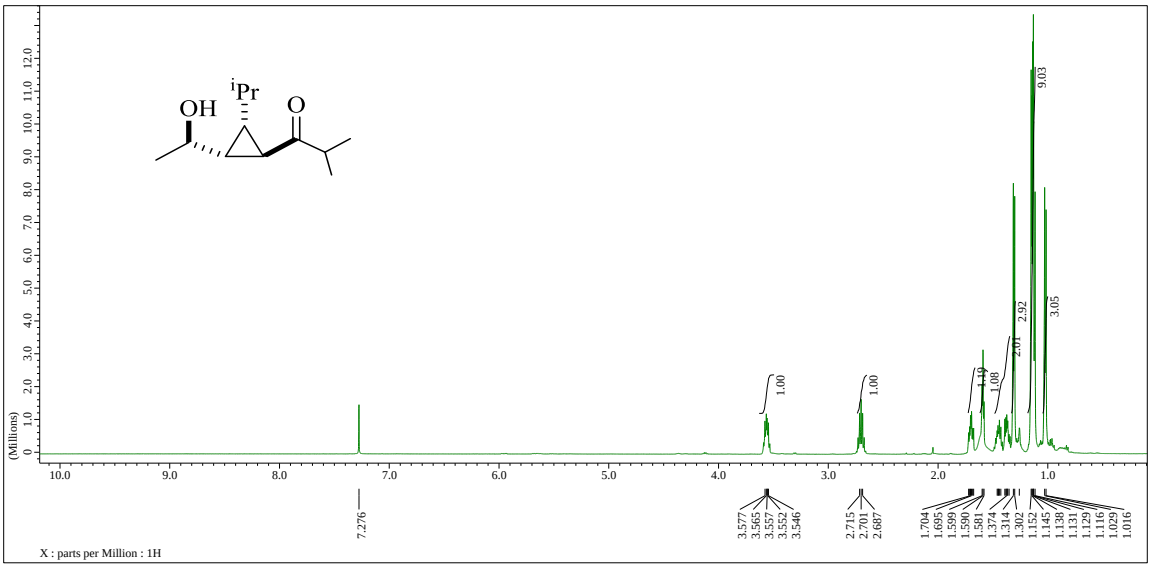

OH
iPr
O
Ph
(Thousands)
X : parts per Million : 13C

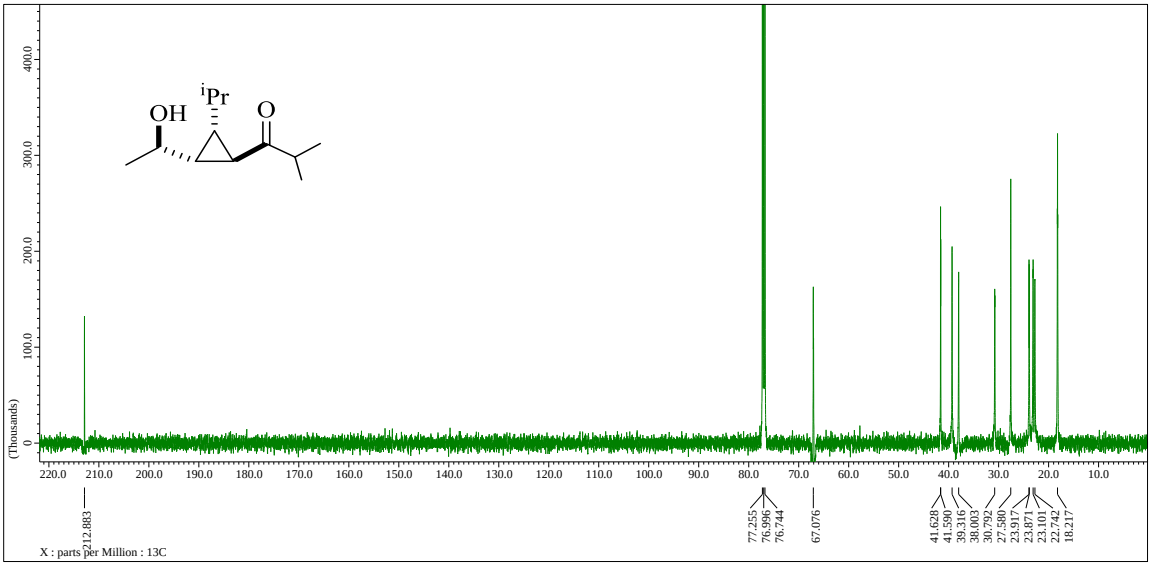

OH
Ph
O
Ph
(Millions)
X : parts per Million : 1H

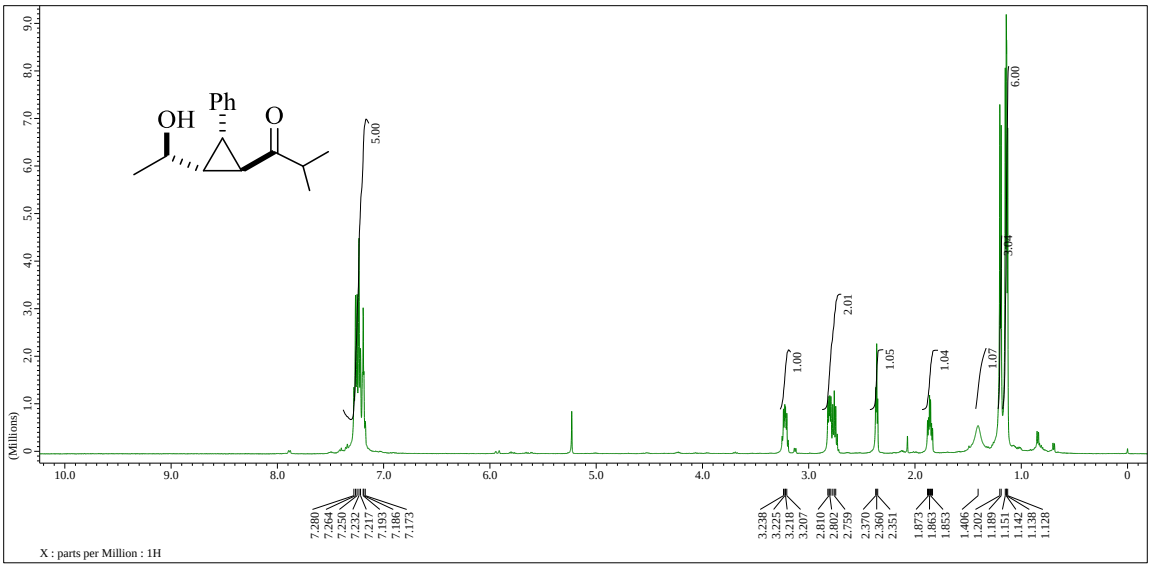

OH
Ph
O
Ph
(Thousands)
X : parts per Million : 13C

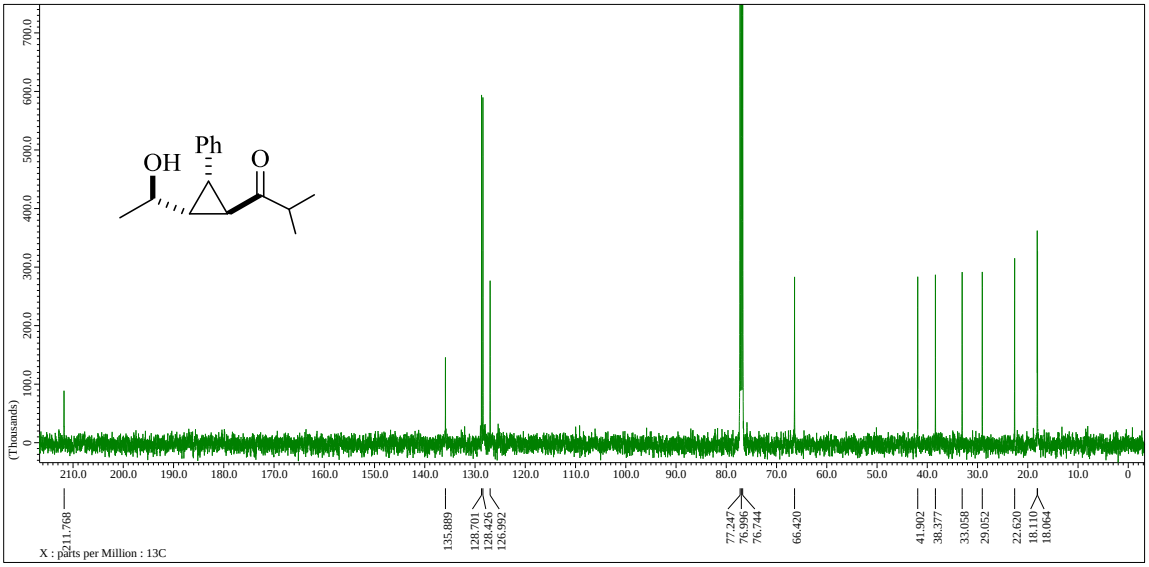

OH
nBu
O
(Millions)
X : parts per Million : 1H
7.274
3.570
3.563
3.557
3.551
3.538
2.723
2.709
2.695
2.681
2.667
1.654
1.595
1.353
1.339
1.325
1.307
1.294
1.136
1.122
0.907
0.892
0.878
1.01
2.70
2.90
0.95
1.06
3.47
4.05
6.09
3.21

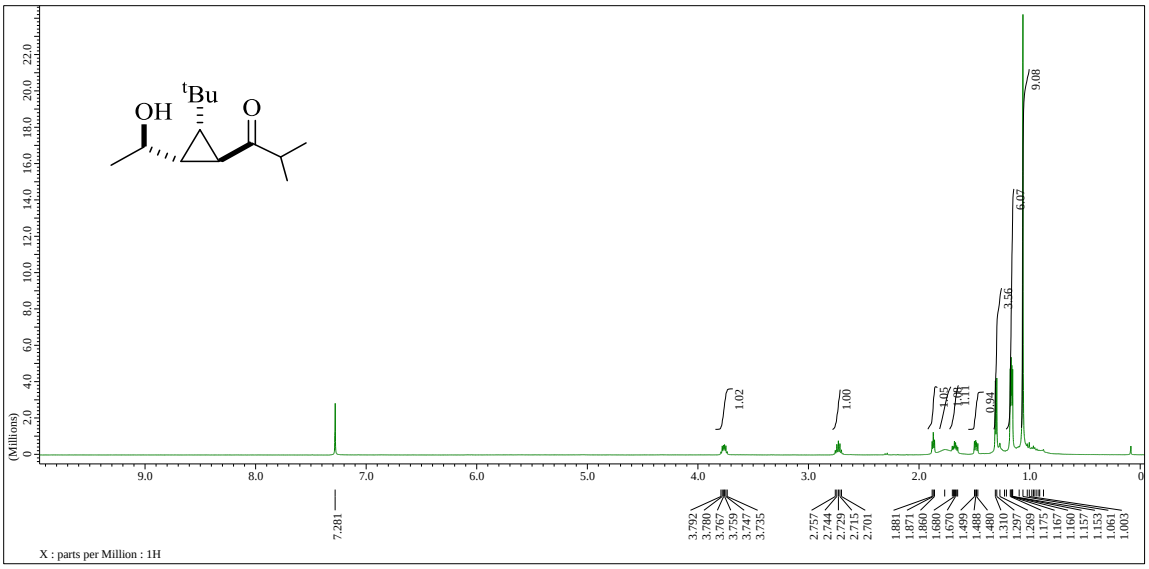

OH
nBu
O
(Millions)
X : parts per Million : 13C
212.878
77.243
76.991
76.739
67.117
41.570
37.251
31.879
31.673
30.574
27.201
23.409
22.402
18.121
13.909

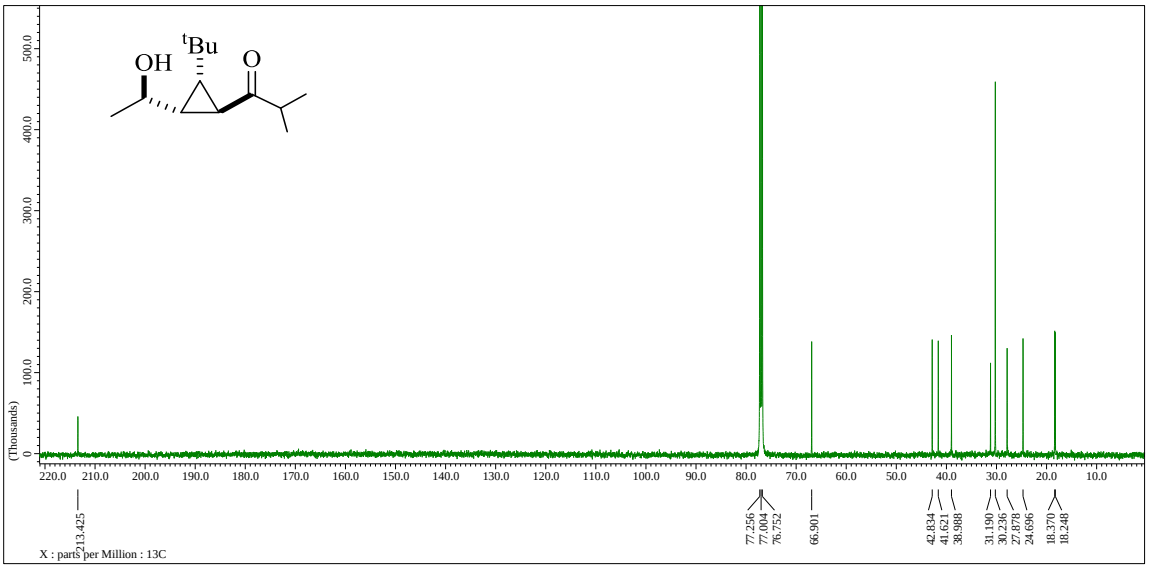

OH
iPr
O
(Millions)
9.03
3.05
2.92
2.01
1.49
1.08
1.00
1.00
7.276
3.577
3.565
3.557
3.552
3.546
2.715
2.701
2.687
1.704
1.695
1.599
1.590
1.581
1.374
1.314
1.302
1.152
1.145
1.138
1.131
1.129
1.116
1.029
1.016
X : parts per Million : 1H

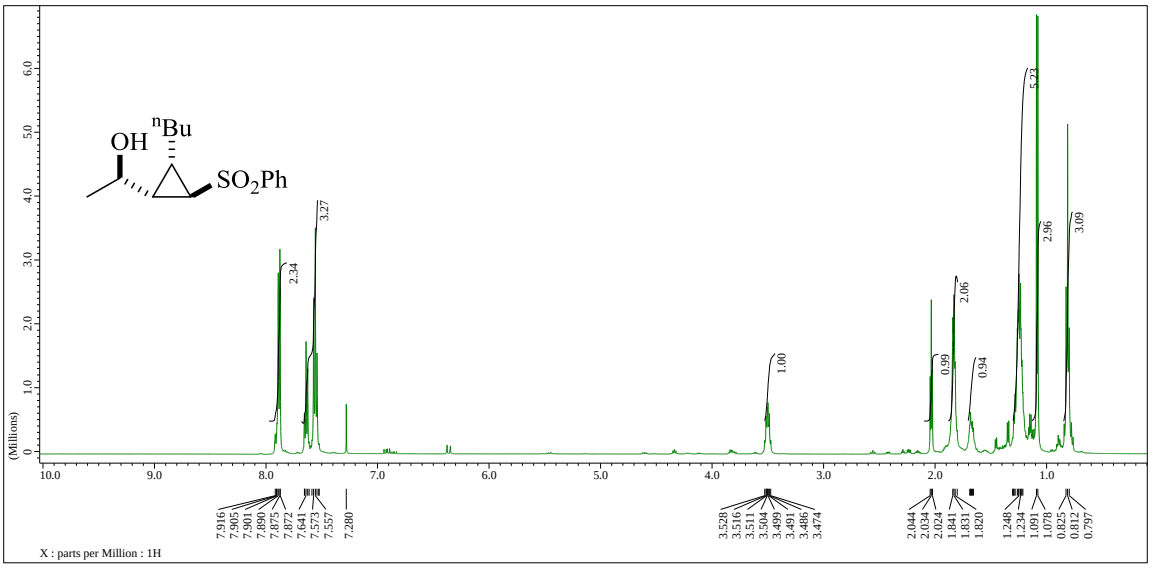

OH
iPr
O
(Thousands)
212.883
77.255
76.996
76.744
67.076
41.628
41.590
39.316
38.003
30.792
27.580
23.917
23.871
23.101
22.742
18.217
X : parts per Million : 13C

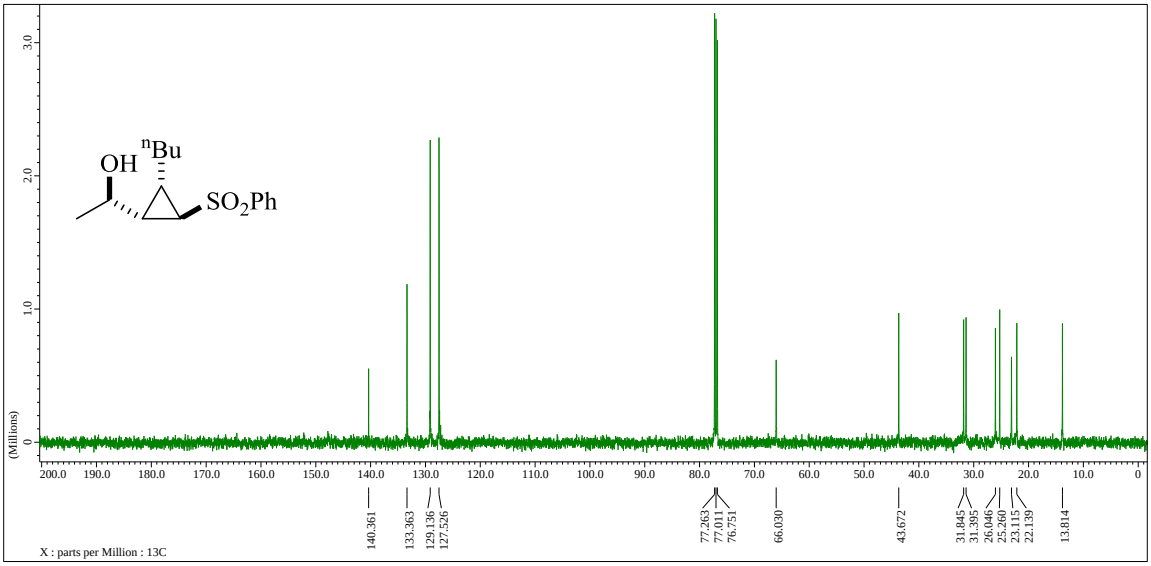

OH
Ph
O
(Millions)
X : parts per Million : 1H

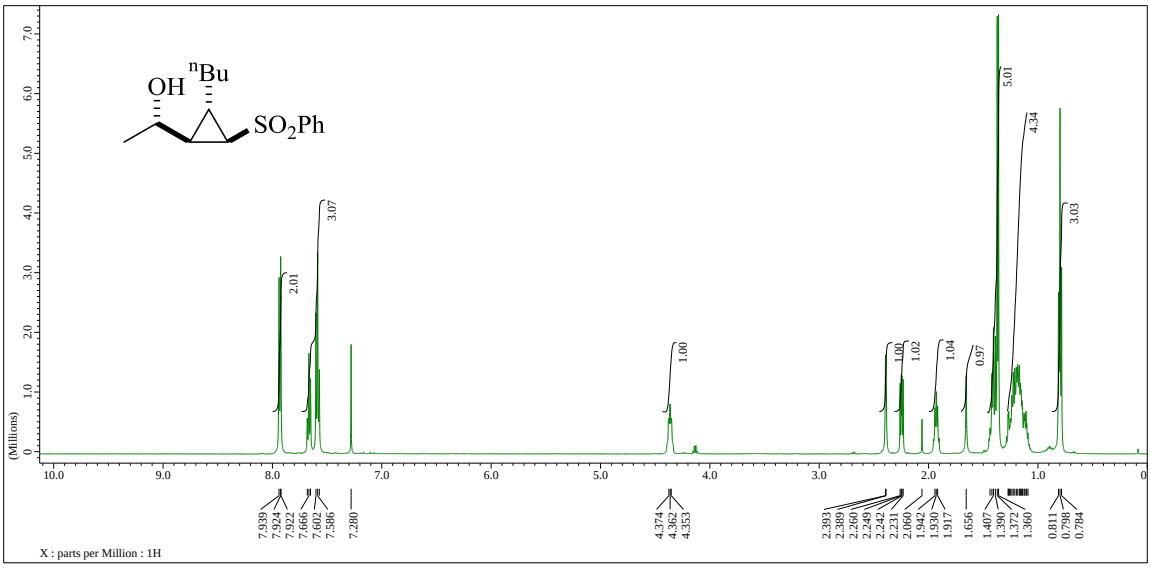

OH
Ph
O
(Thousands)
X : parts per Million : 13C

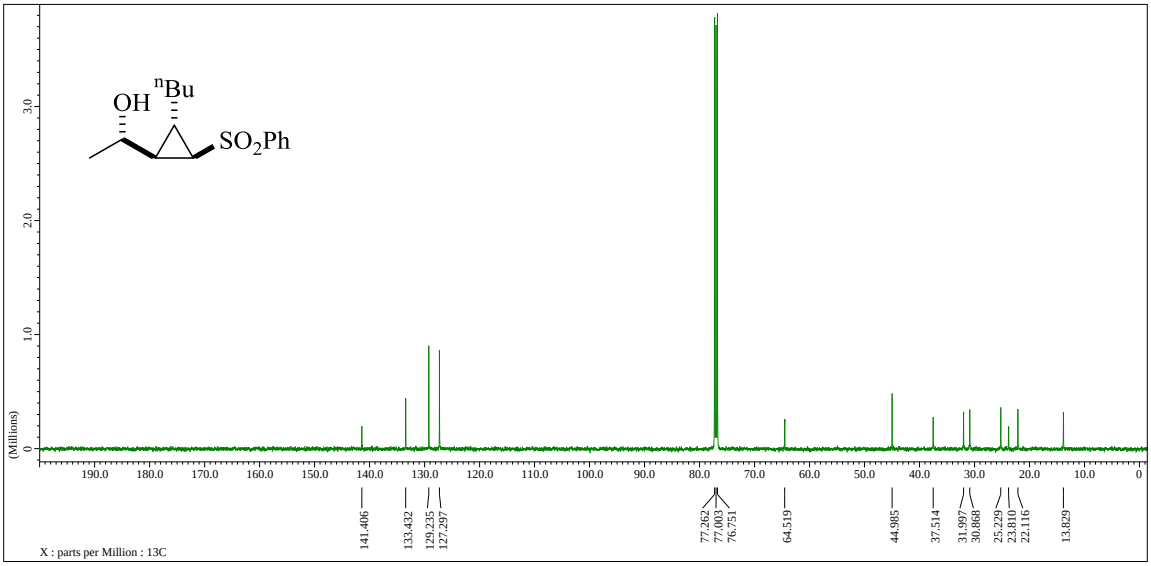

OH
tBu
O
(Millions)
9.08
6.07
3.56
1.02
1.00
1.05
1.04
1.01
0.94
7.281
3.792
3.780
3.767
3.759
3.747
3.735
2.757
2.744
2.729
2.715
2.701
1.881
1.871
1.860
1.680
1.670
1.499
1.488
1.480
1.310
1.297
1.269
1.175
1.167
1.160
1.157
1.153
1.061
1.003
X : parts per Million : 1H

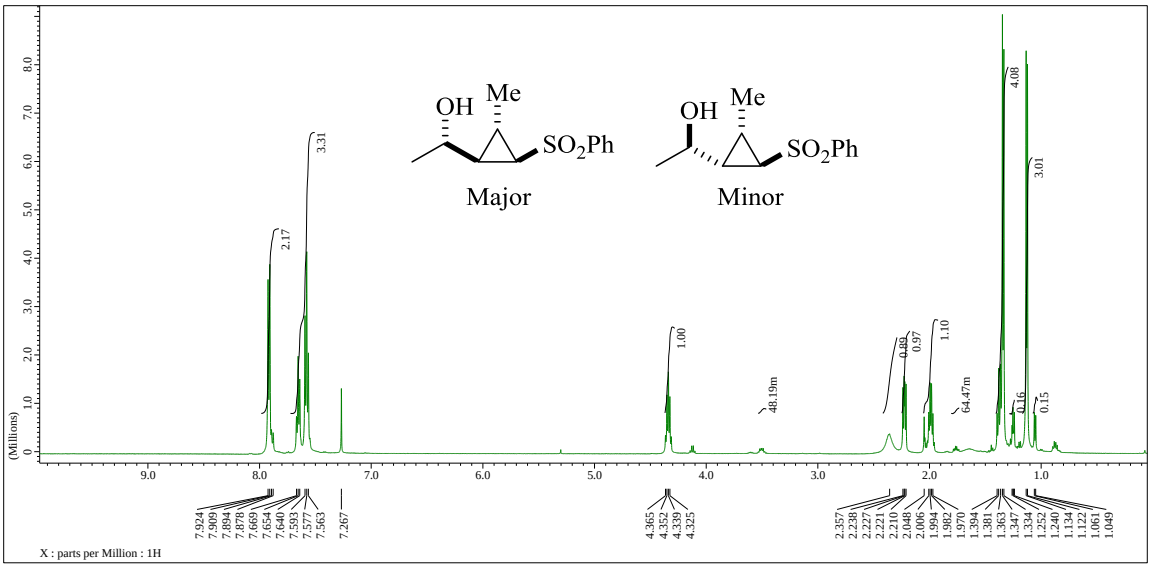

OH
tBu
O
(Thousands)
213.425
77.256
77.004
76.752
66.901
42.834
41.621
38.988
31.190
30.236
27.878
24.696
18.370
18.248
X : parts per Million : 13C

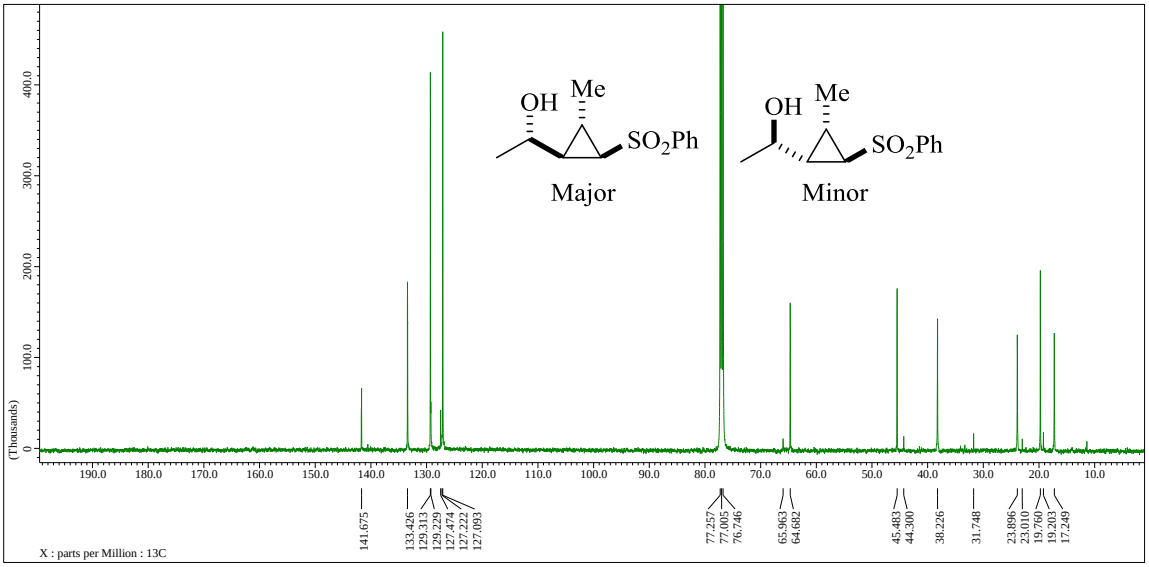

OH
nBu
SO2Ph
(Millions)
X : parts per Million : 1H

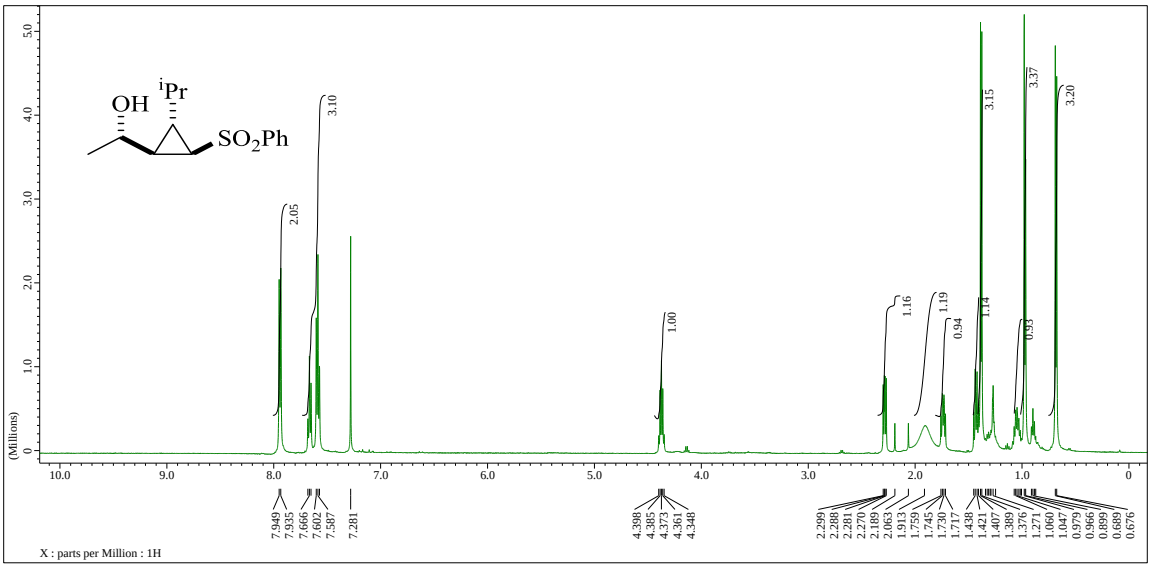

OH
nBu
SO2Ph
(Millions)
X : parts per Million : 13C

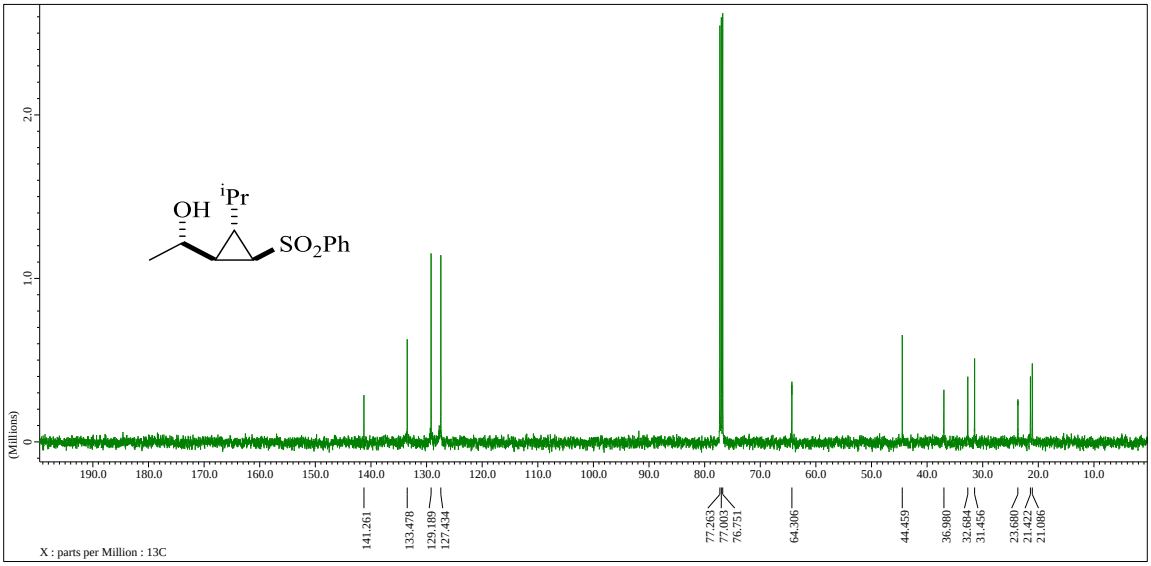

OH
nBu
SO2Ph
(Millions)
X : parts per Million : 1H

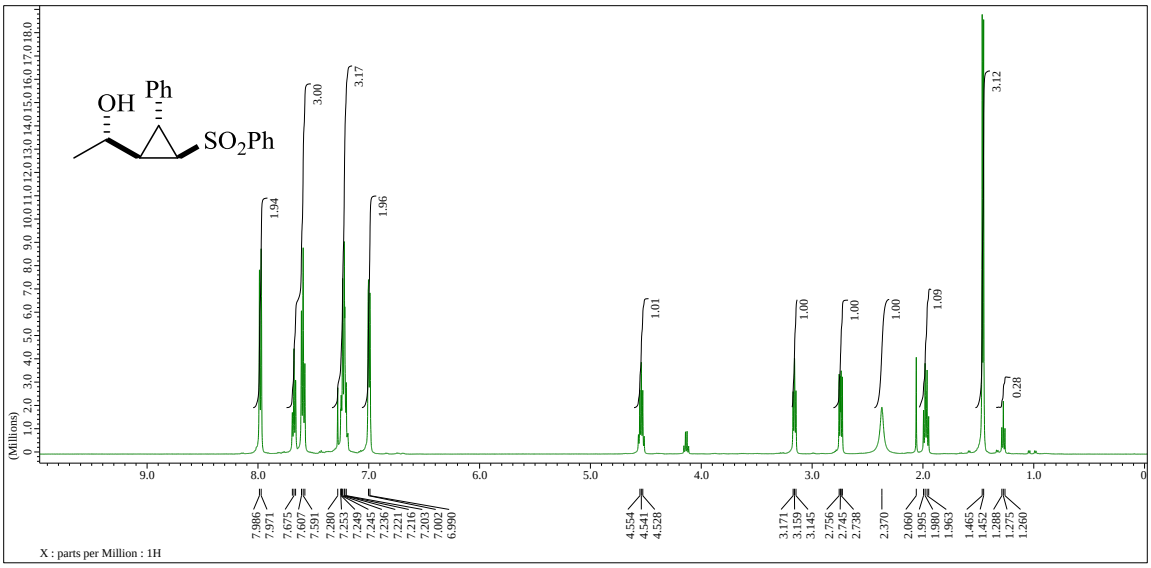

OH
nBu
SO2Ph
(Millions)
X : parts per Million : 13C

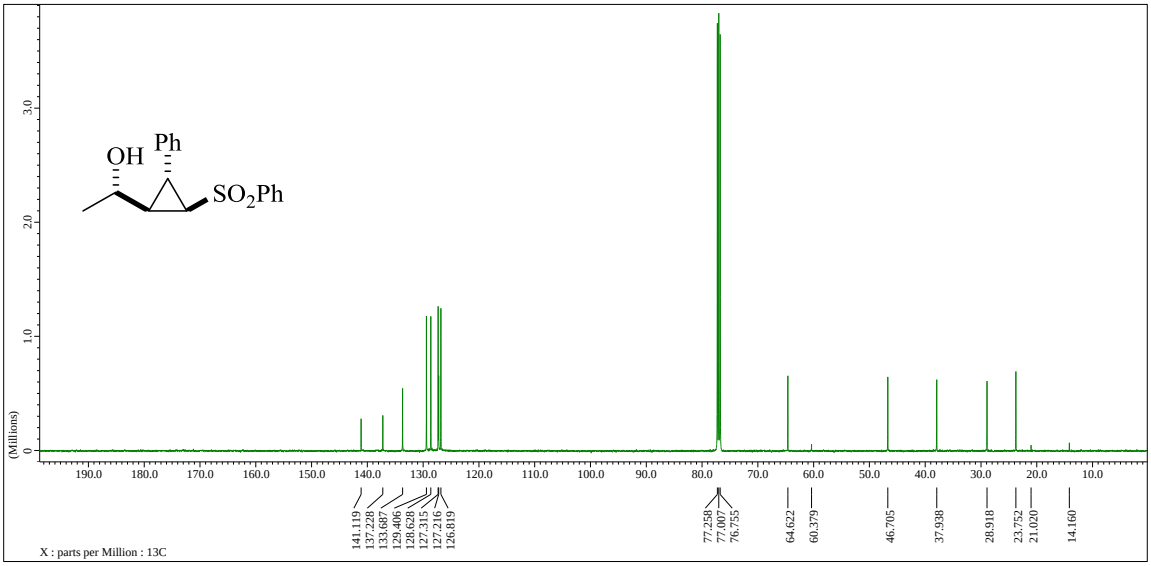

OH
Me
SO2Ph
Major
OH
Me
SO2Ph
Minor
(Millions)
X : parts per Million : 1H

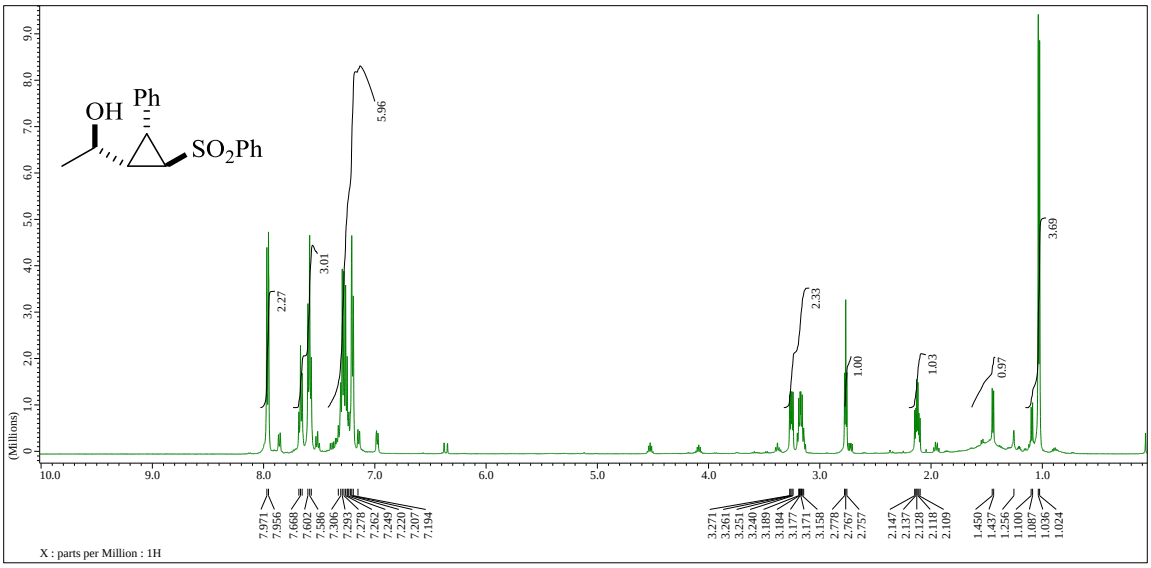

OH
Me
SO2Ph
Major
OH
Me
SO2Ph
Minor
(Thousands)
X : parts per Million : 13C

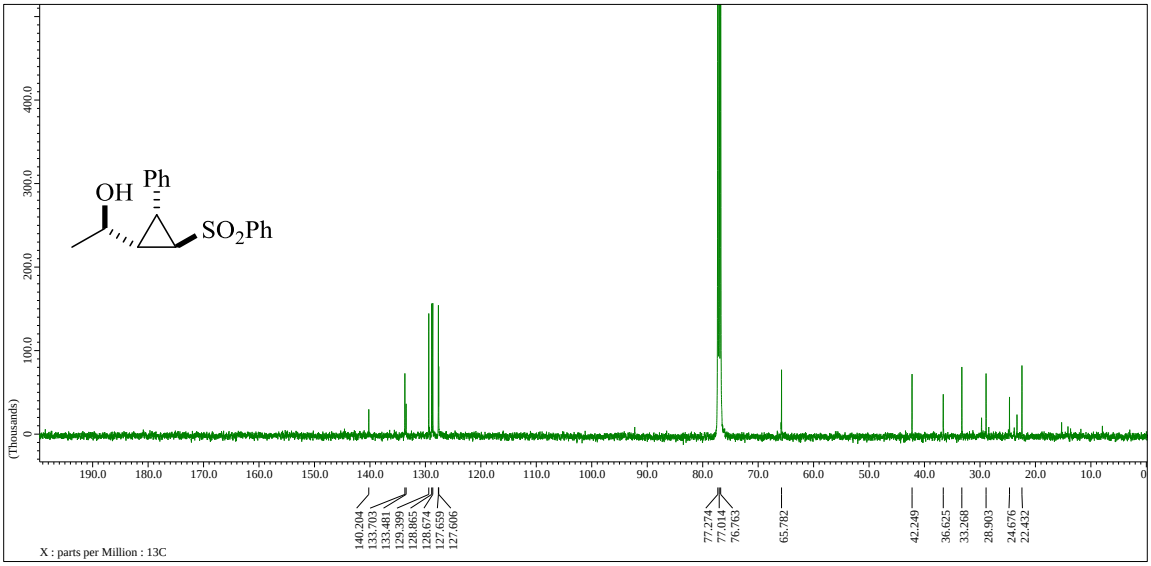

OH
iPr
SO2Ph
(Millions)
X : parts per Million : 1H

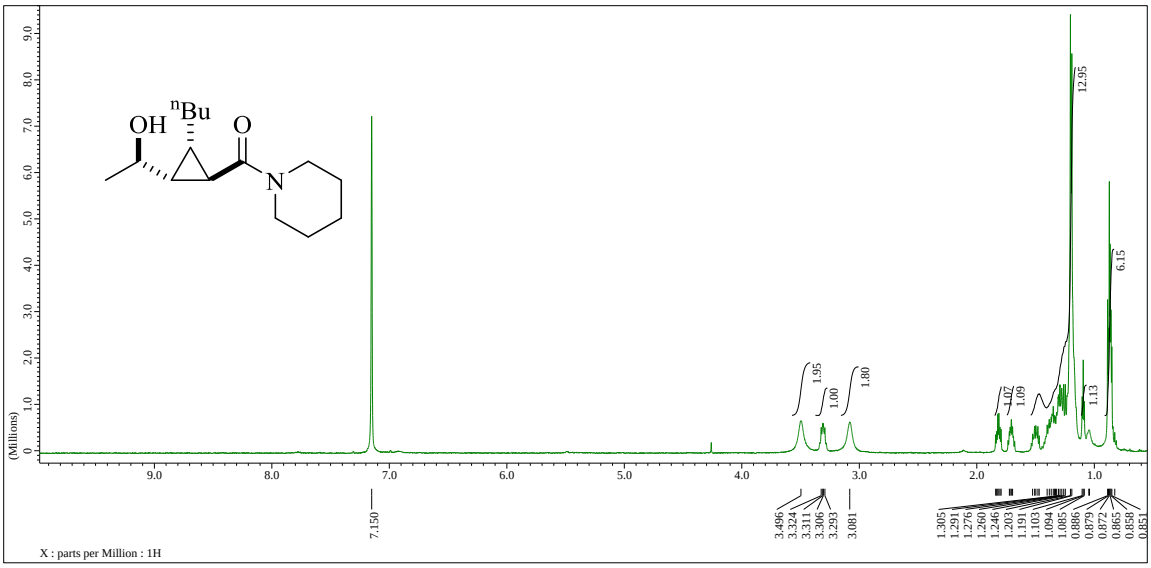

OH
iPr
SO2Ph
(Millions)
X : parts per Million : 13C

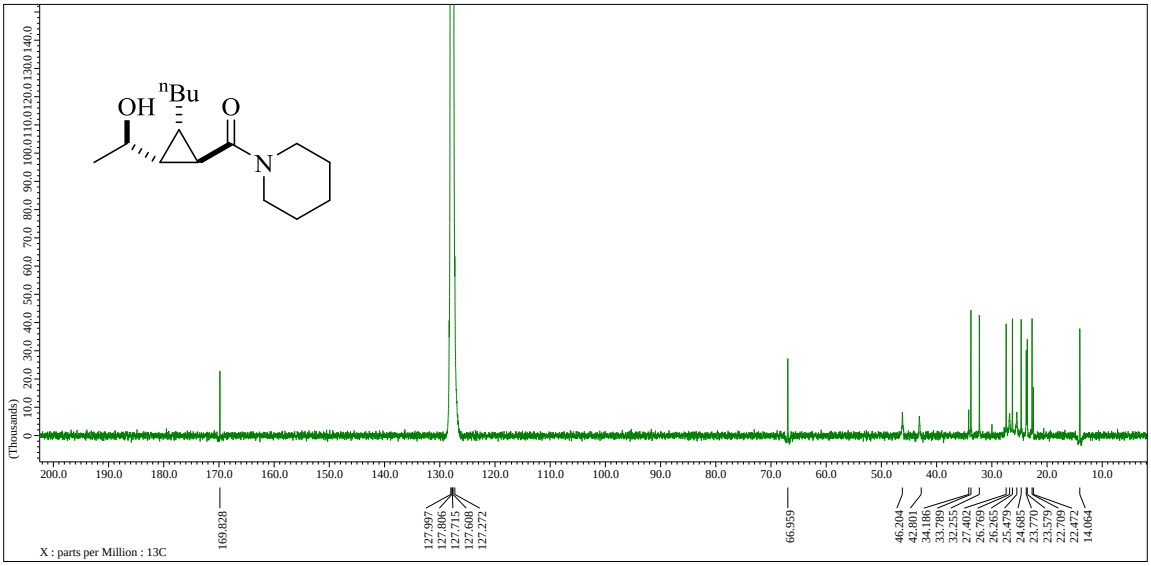

OH
Ph
SO2Ph
1.94
3.00
3.17
1.96
1.01
1.00
1.00
1.00
1.09
3.12
0.28
7.986
7.971
7.675
7.607
7.591
7.280
7.253
7.249
7.245
7.236
7.221
7.216
7.203
7.002
6.990
4.554
4.541
4.528
3.171
3.159
3.145
2.756
2.745
2.738
2.370
2.060
1.995
1.980
1.963
1.465
1.432
1.288
1.275
1.260
(Millions)
X : parts per Million : 1H

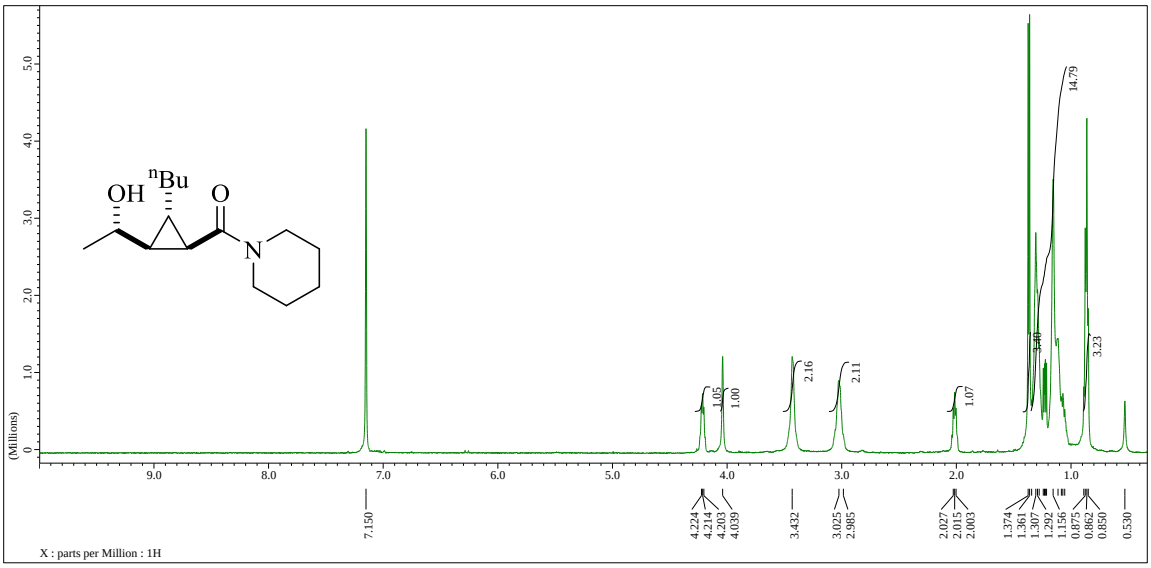

OH
Ph
SO2Ph
141.119
137.228
133.687
129.406
128.628
127.315
127.216
126.819
77.258
77.007
76.755
64.622
60.379
46.705
37.938
28.918
23.752
21.020
14.160
(Millions)
X : parts per Million : 13C

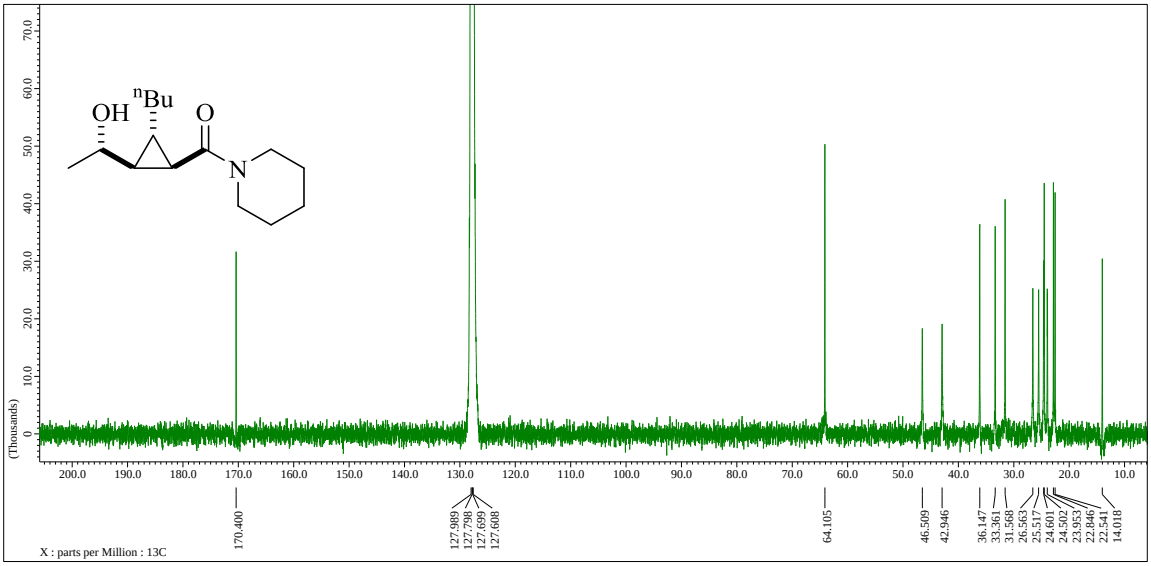

OH
Ph
SO2Ph
5.96
3.01
2.27
2.33
1.00
1.03
0.97
3.69
(Millions)
X : parts per Million : 1H

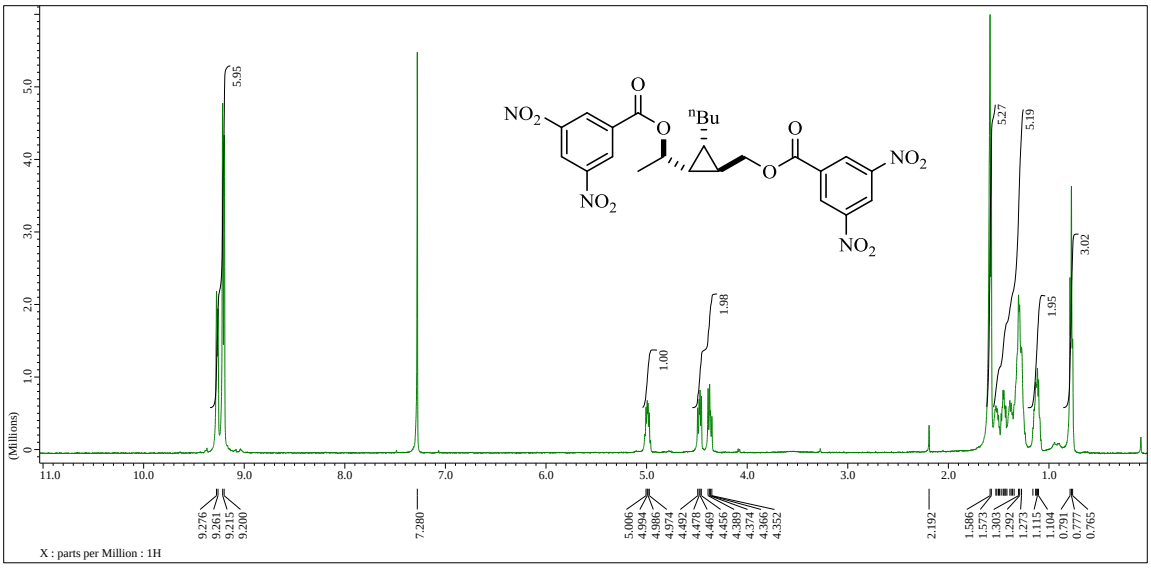

OH
Ph
SO2Ph
(Thousands)
X : parts per Million : 13C

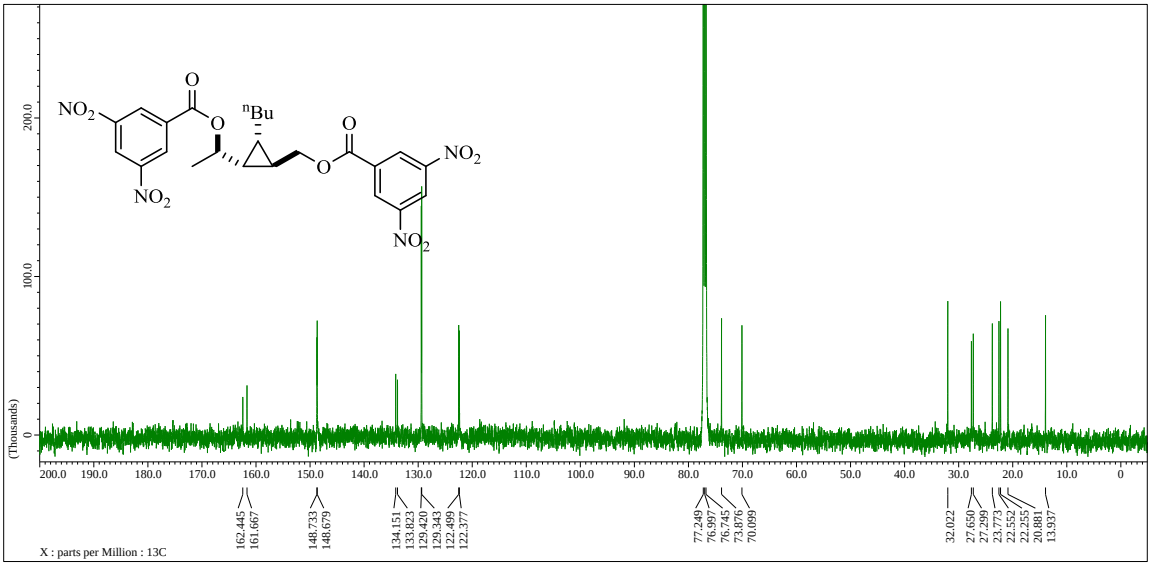

OH
nBu
O
N
(Millions)
12.95
6.15
1.95
1.00
1.80
1.07
1.09
1.13
7.150
3.496
3.324
3.311
3.306
3.293
3.081
1.305
1.291
1.276
1.260
1.246
1.203
1.191
1.103
1.094
1.085
0.886
0.879
0.872
0.865
0.858
0.851
X : parts per Million : 1H

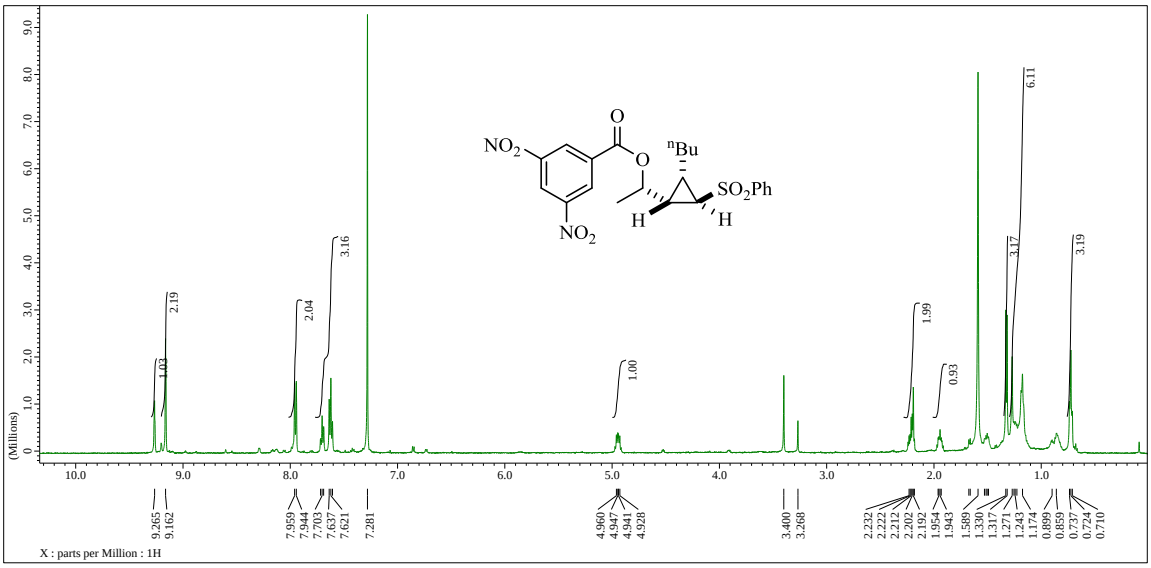

OH
nBu
O
N
(Thousands)
169.828
127.997
127.806
127.715
127.608
127.272
66.959
46.204
42.801
34.186
33.789
32.255
27.402
26.769
26.565
25.476
24.685
23.770
23.579
22.709
22.472
14.064
X : parts per Million : 13C

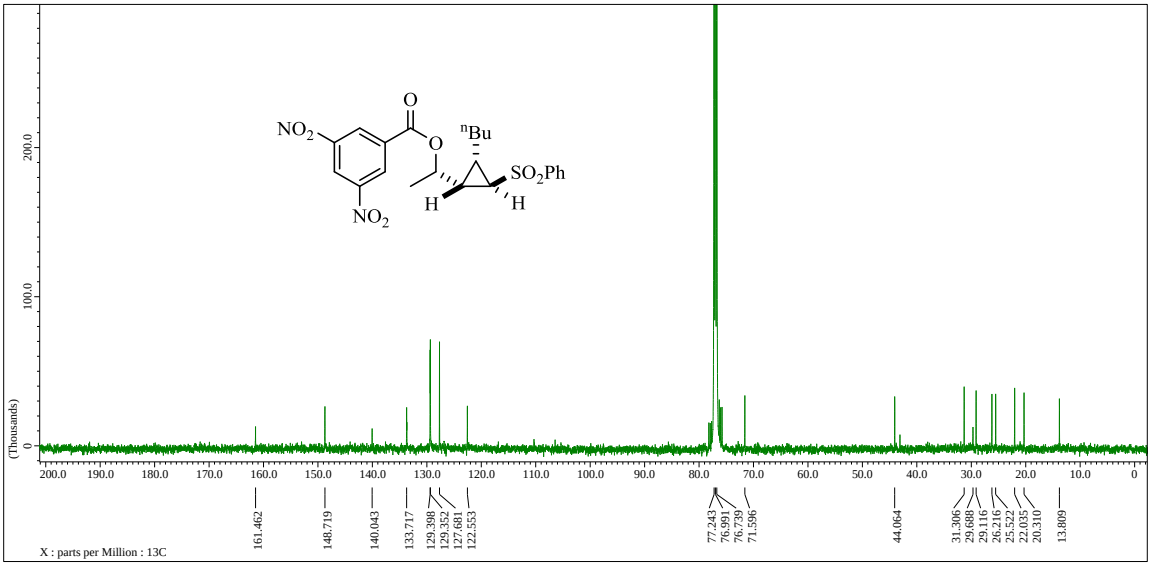

OH
nBu
O
N
(Millions)
X : parts per Million : 1H

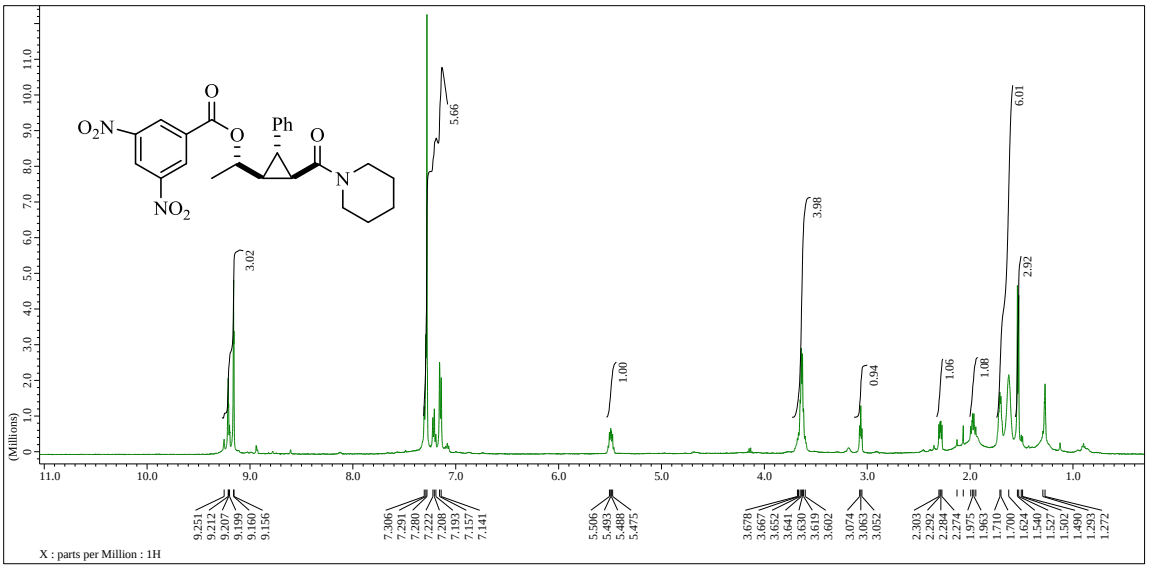

OH
nBu
O
N
(Thousands)
X : parts per Million : 13C

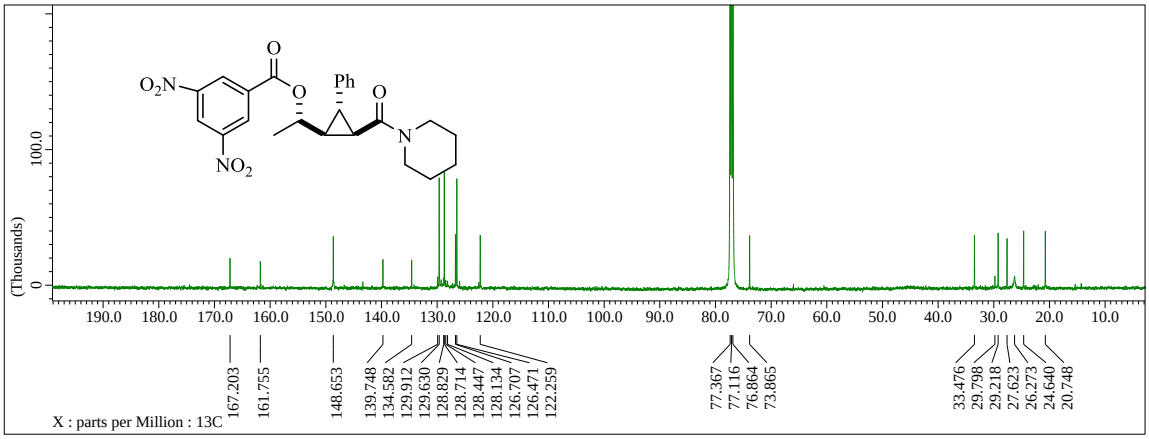

(Millions)
X : parts per Million : 1H

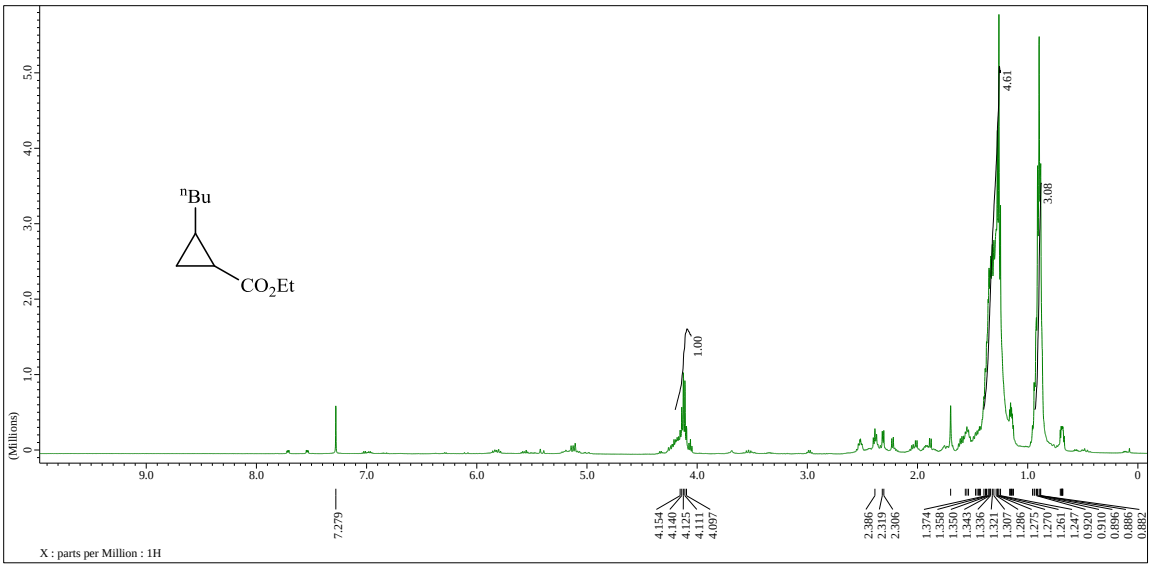

(Thousands)
X : parts per Million : 13C

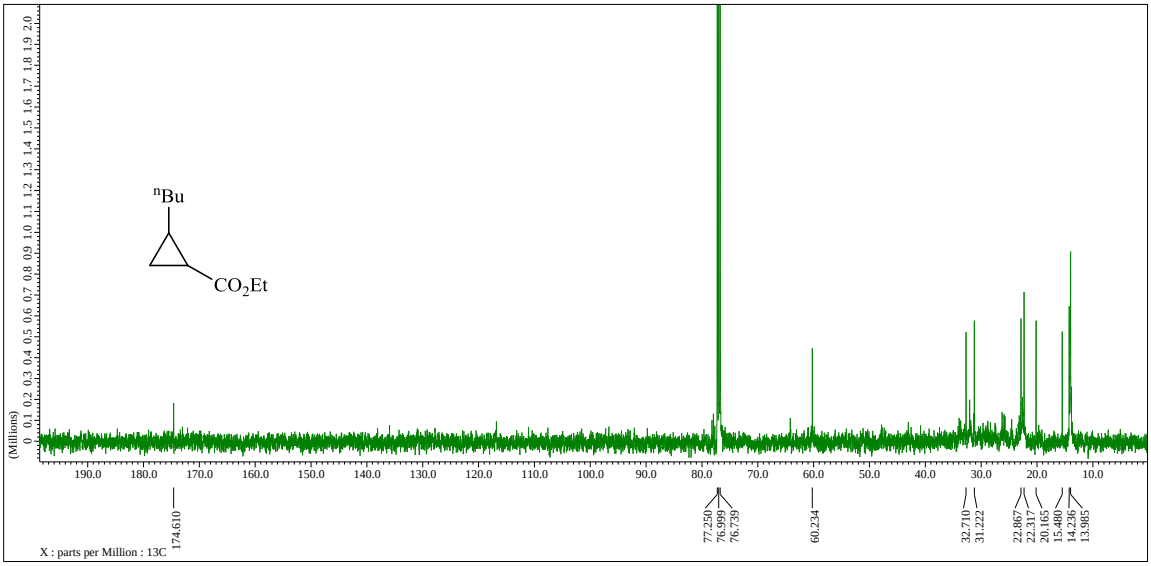

NO2
O
O
nBu
SO2Ph
H
H
NO2
(Millions)
X : parts per Million : 1H

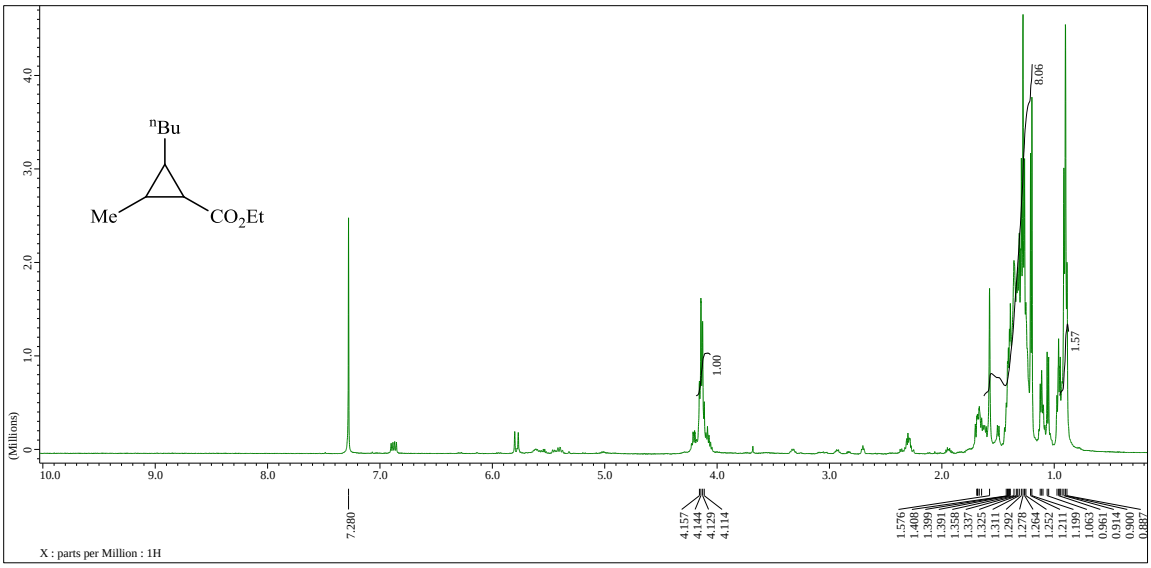

NO2
O
O
nBu
SO2Ph
H
H
NO2
(Thousands)
X : parts per Million : 13C

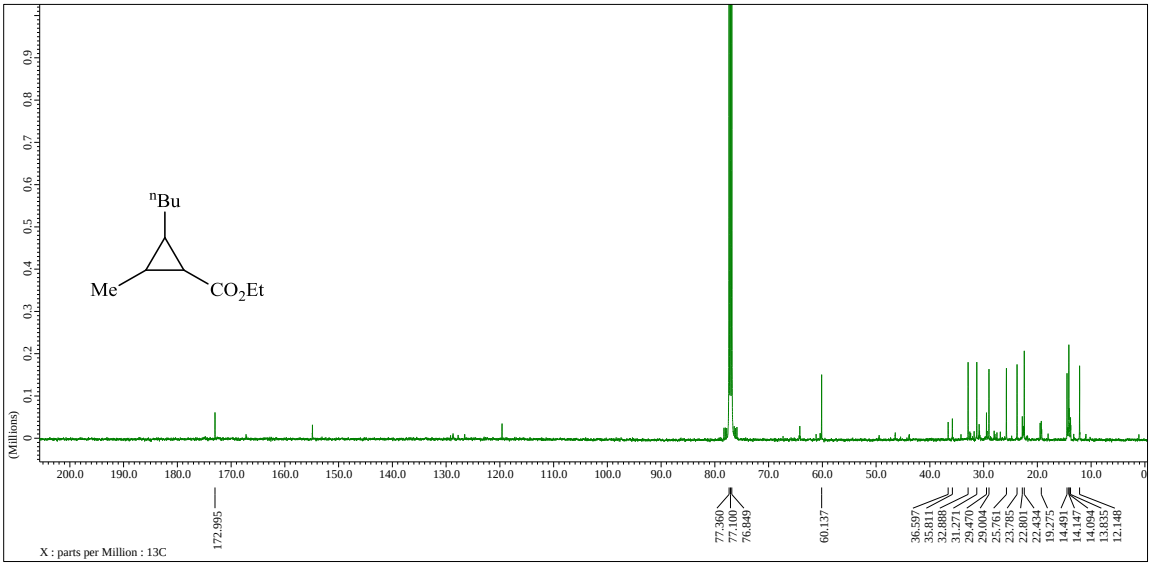

(Millions)
X : parts per Million : 1H

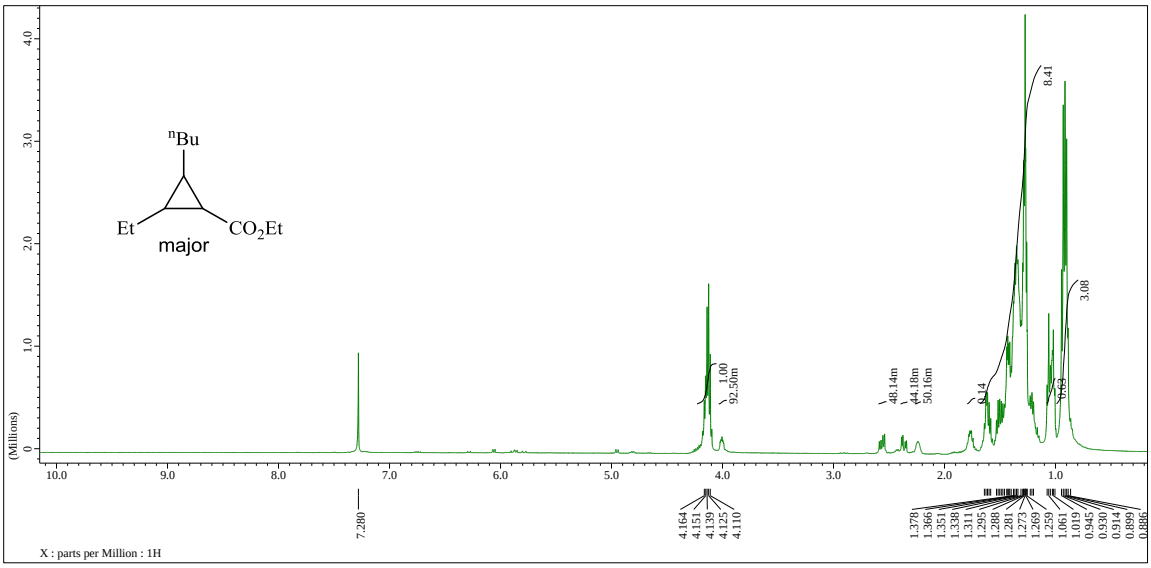

(Thousands)
X : parts per Million : 13C

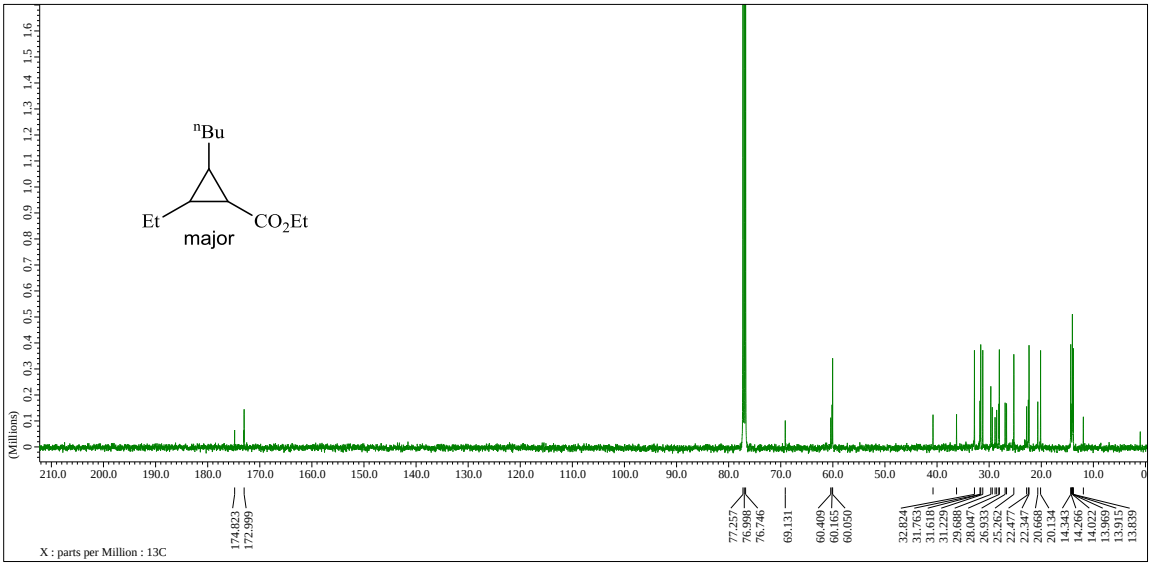

nBu
CO2Et
4.61
3.08
1.00
(Millions)
X : parts per Million : 1H

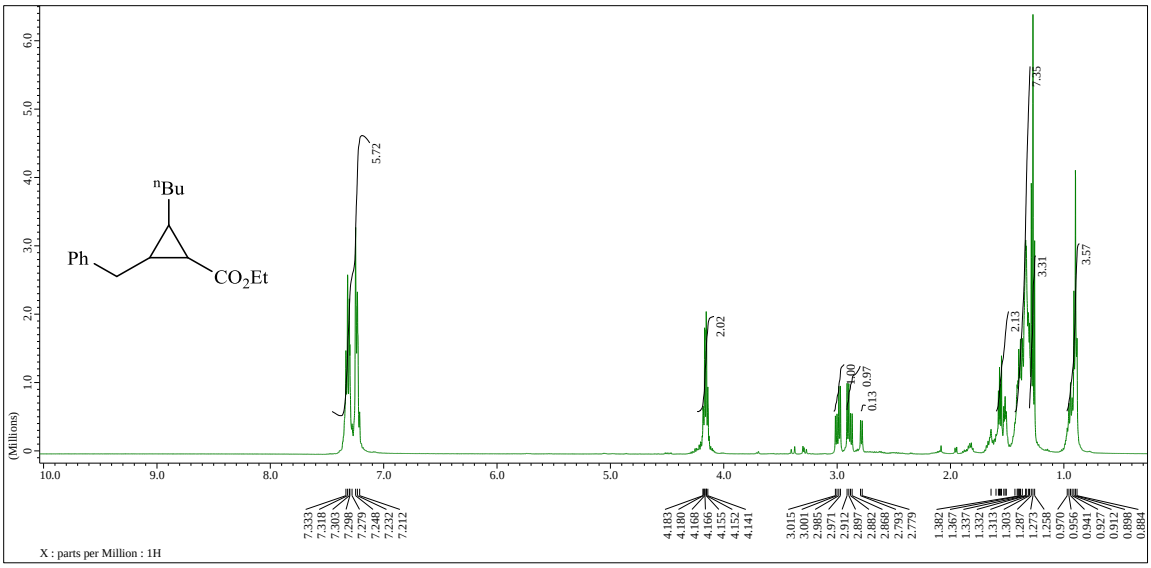

nBu
CO2Et
(Millions)
X : parts per Million : 13C

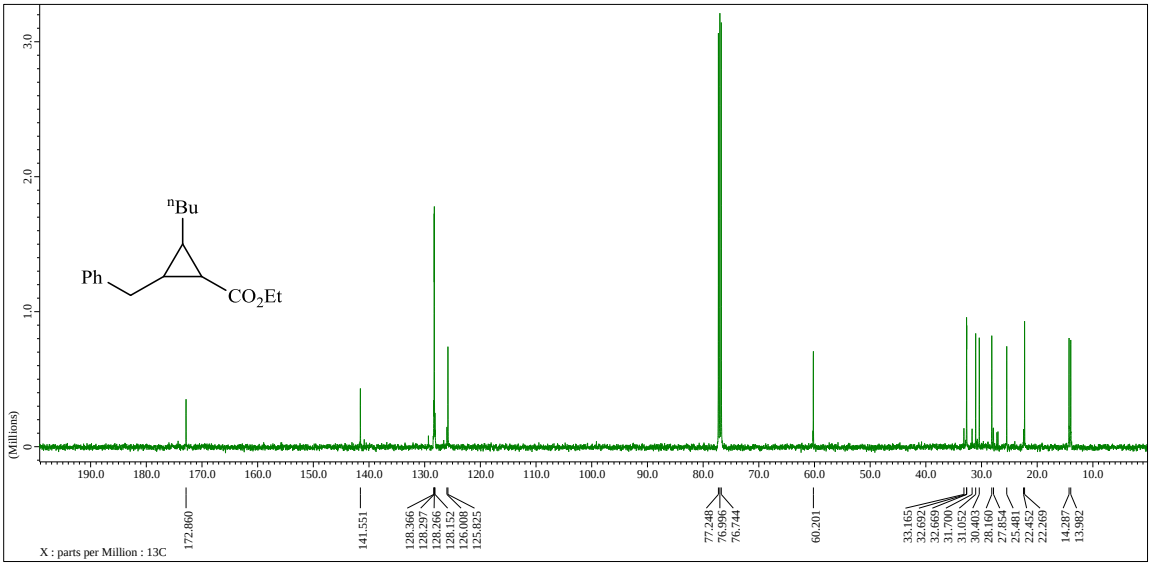

nBu
Me
CO2Et
8.06
1.57
1.00
(Millions)
7.280
4.157
4.144
4.129
4.114
1.576
1.408
1.399
1.391
1.358
1.337
1.325
1.311
1.292
1.278
1.264
1.251
1.211
1.199
1.063
0.961
0.914
0.900
0.887
X : parts per Million : 1H

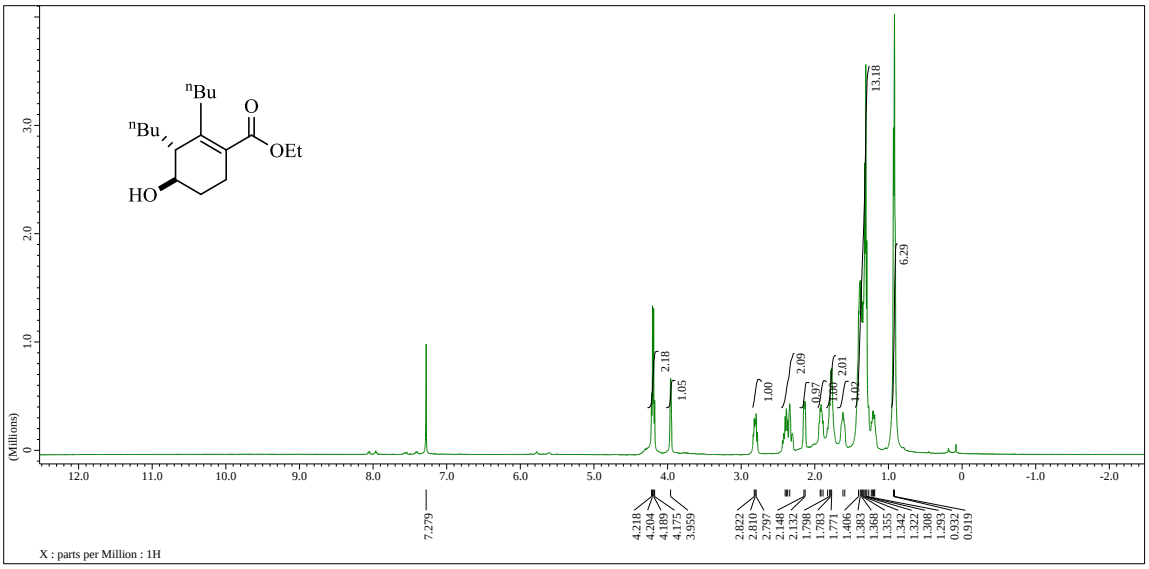

nBu
Me
CO2Et
(Millions)
172.995
77.360
77.100
76.849
60.137
36.597
35.811
32.888
31.271
29.470
29.004
25.761
23.785
22.801
22.434
19.275
14.491
14.147
14.094
13.835
12.148
X : parts per Million : 13C

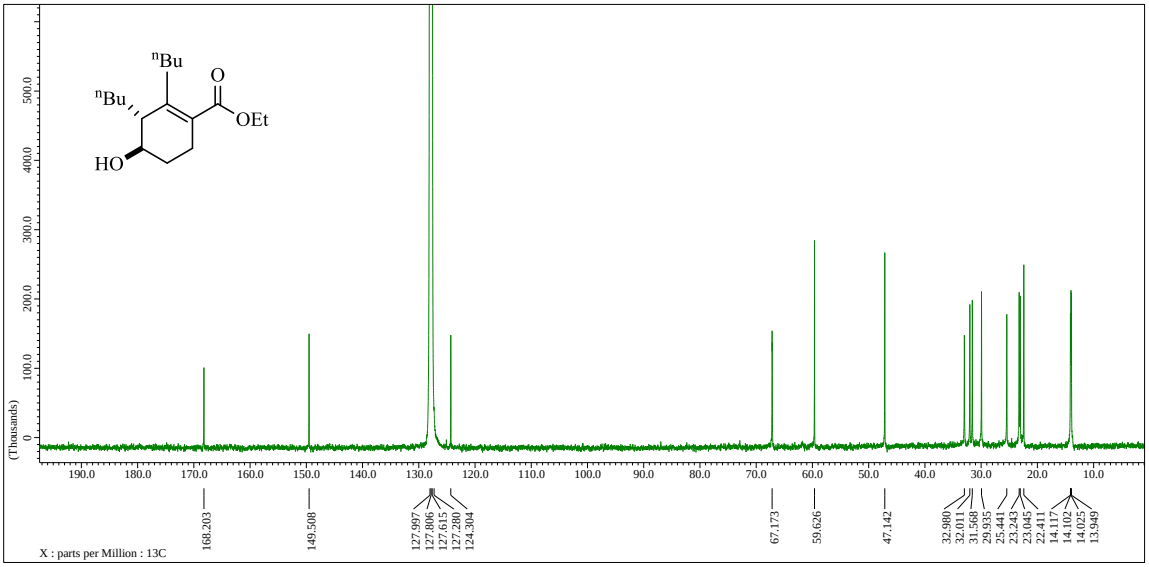

nBu
Et
CO2Et
major
(Millions)
8.41
3.08
1.00
92.50m
48.14m
44.18m
50.16m
7.280
4.164
4.151
4.139
4.125
4.110
1.378
1.366
1.351
1.338
1.311
1.295
1.288
1.281
1.273
1.269
1.259
1.061
1.019
0.945
0.930
0.914
0.899
0.886
X : parts per Million : 1H

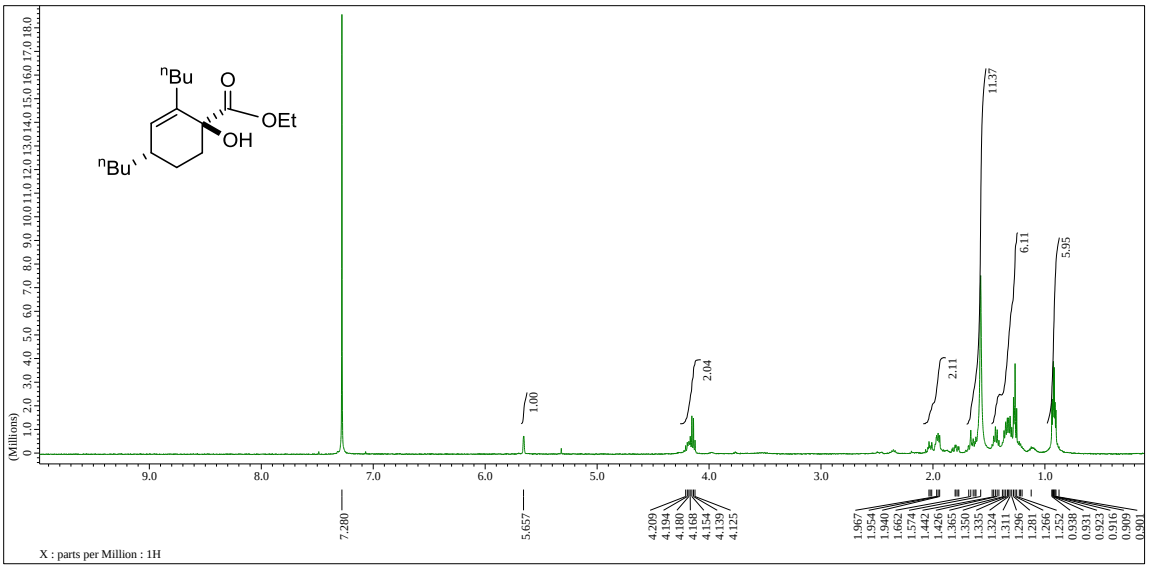

nBu
Et
CO2Et
major
(Millions)
174.823
172.999
77.257
76.998
76.746
69.131
60.409
60.165
60.050
32.824
31.763
31.618
31.229
29.688
28.047
26.933
25.262
22.477
22.347
20.668
20.134
14.345
14.266
14.072
13.965
13.915
13.839
X : parts per Million : 13C

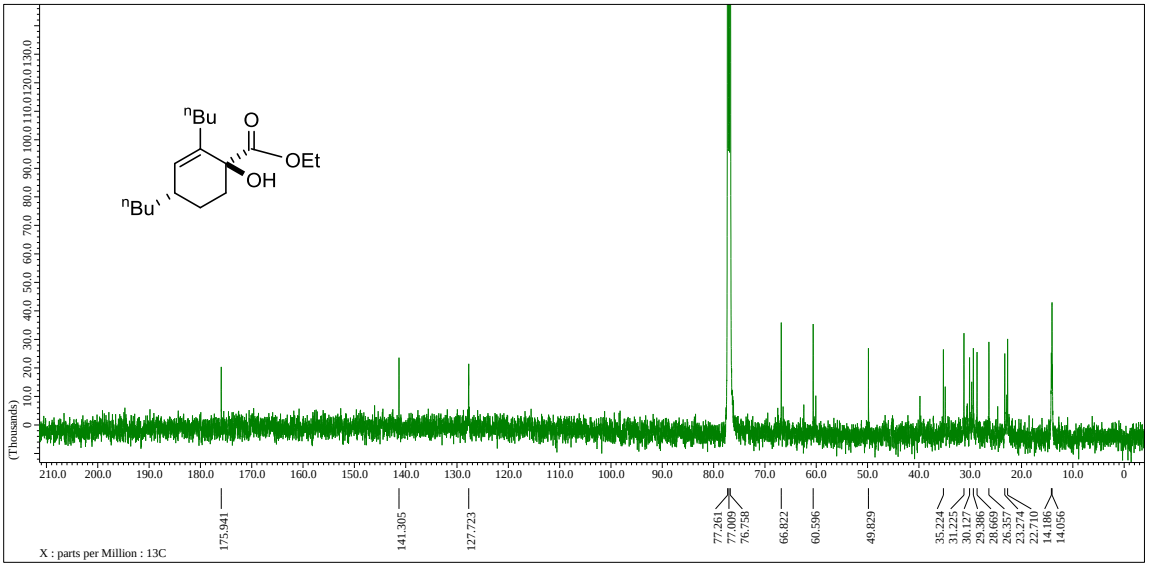

nBu
Ph
CO2Et
5.72
2.02
1.40
0.97
0.13
2.13
7.35
3.31
3.57
(Millions)
X : parts per Million : 1H

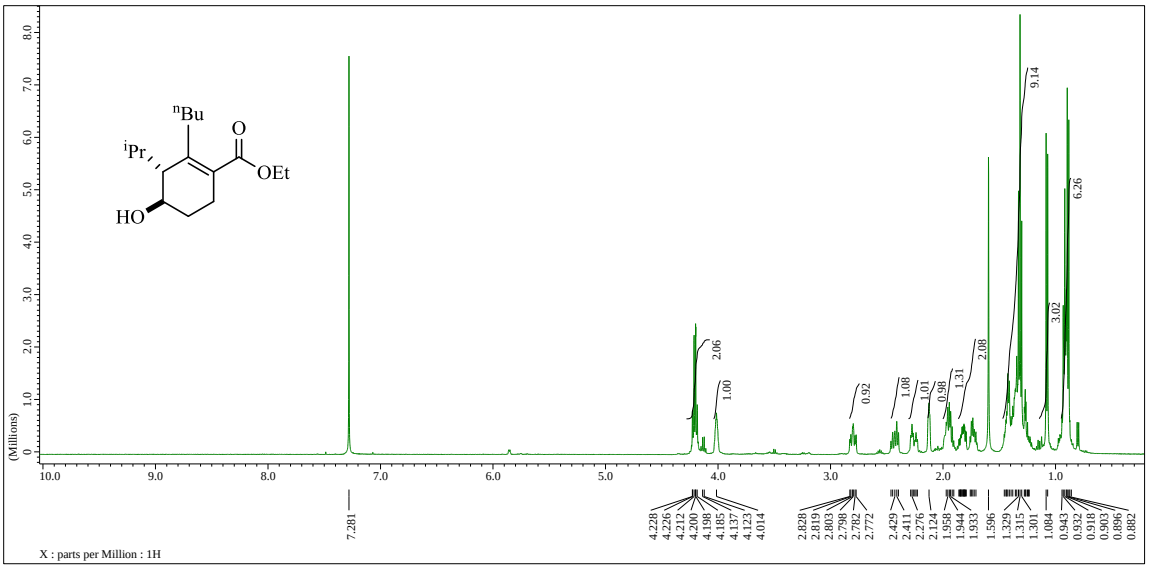

nBu
Ph
CO2Et
(Millions)
X : parts per Million : 13C

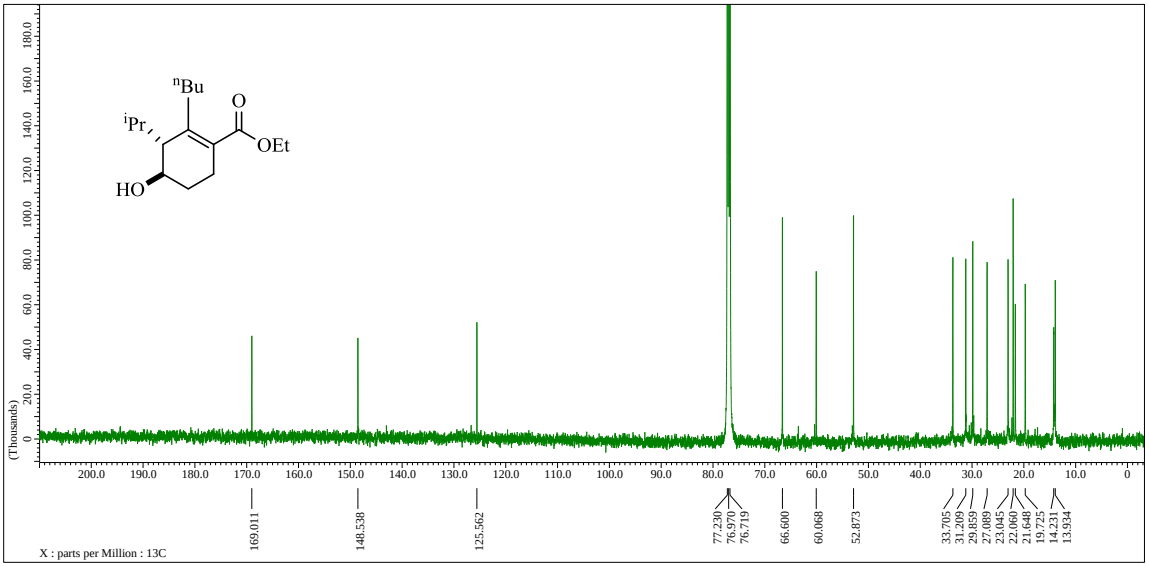

nBu
nBu
O
OEt
HO
(Millions)
3.0
2.0
1.0
0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
-2.0
13.18
6.29
2.18
1.05
1.00
2.09
0.97
1.60
2.01
1.02
7.279
4.218
4.204
4.189
4.175
3.959
2.822
2.810
2.797
2.148
2.132
1.798
1.783
1.771
1.406
1.383
1.368
1.355
1.342
1.322
1.308
1.293
0.932
0.919
X : parts per Million : 1H

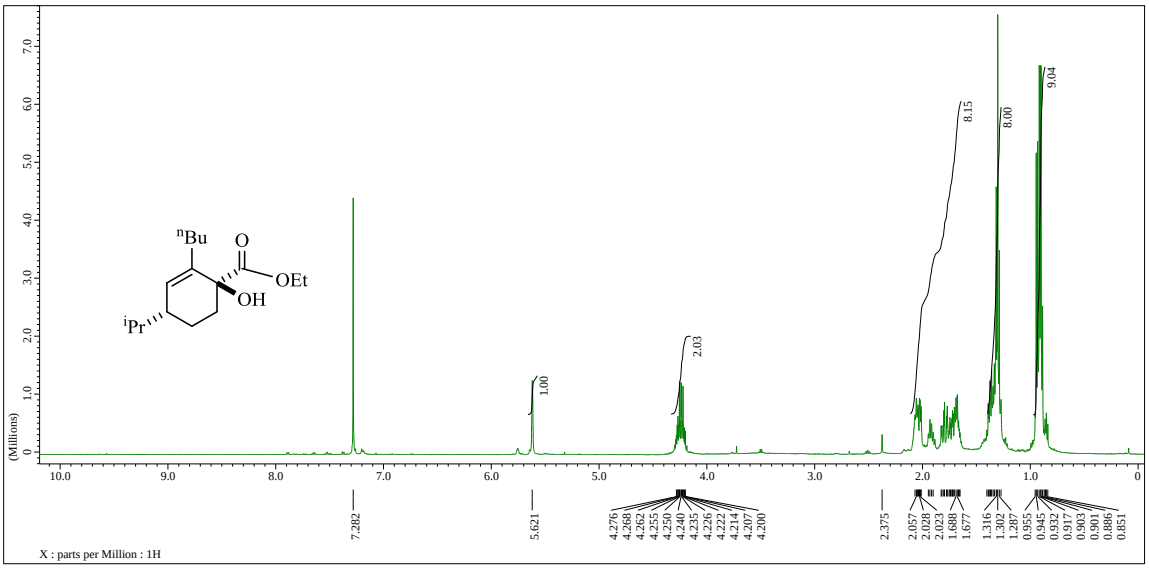

nBu
nBu
O
OEt
HO
(Thousands)
500.0
400.0
300.0
200.0
100.0
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
168.203
149.508
127.997
127.806
127.615
127.280
124.304
67.173
59.626
47.142
32.980
32.011
31.568
29.935
25.441
23.243
23.045
22.411
14.117
14.102
14.025
13.949
X : parts per Million : 13C

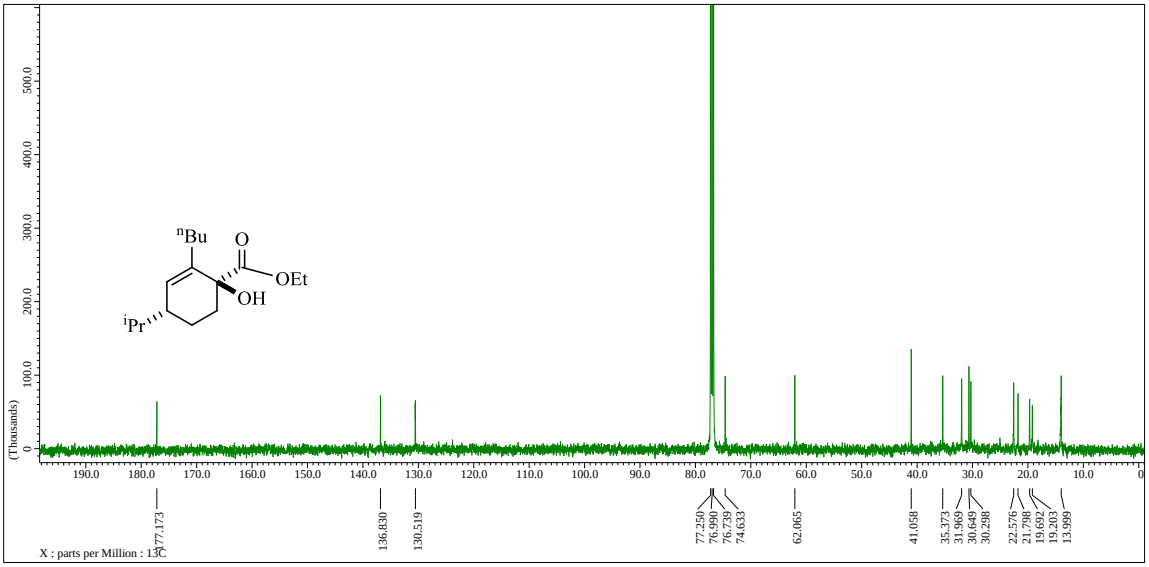

nBu
O
OEt
OH
nBu
(Millions)
11.37
6.11
5.95
2.11
2.04
1.00
7.280
5.657
4.209
4.194
4.180
4.168
4.154
4.139
4.125
1.967
1.954
1.940
1.662
1.574
1.442
1.426
1.365
1.350
1.335
1.324
1.311
1.296
1.281
1.266
1.252
0.938
0.931
0.923
0.916
0.909
0.901
X : parts per Million : 1H

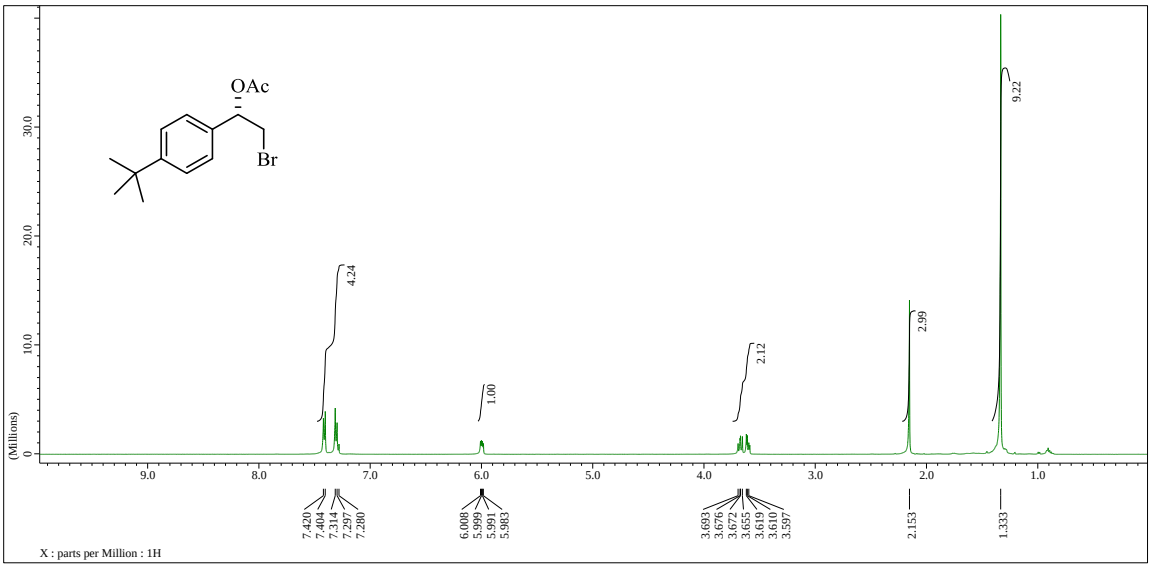

nBu
O
OEt
OH
nBu
(Thousands)
175.941
141.305
127.723
77.261
77.009
76.758
66.822
60.596
49.829
35.224
31.225
30.127
29.386
28.669
26.357
23.274
22.710
14.186
14.056
X : parts per Million : 13C

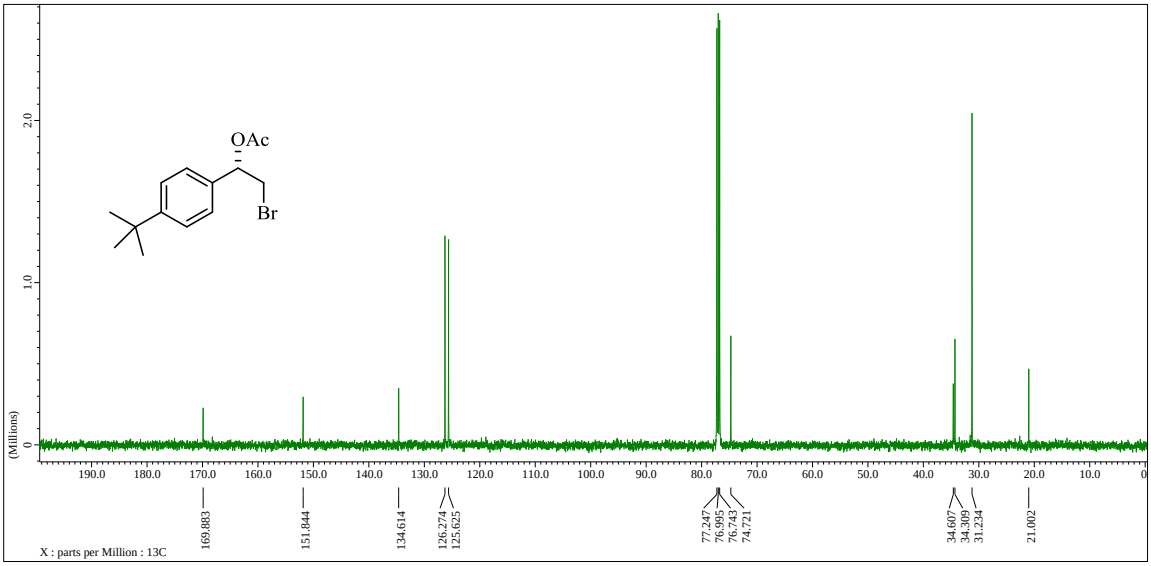

nBu
iPr
O
OEt
HO
(Millions)
X : parts per Million : 1H

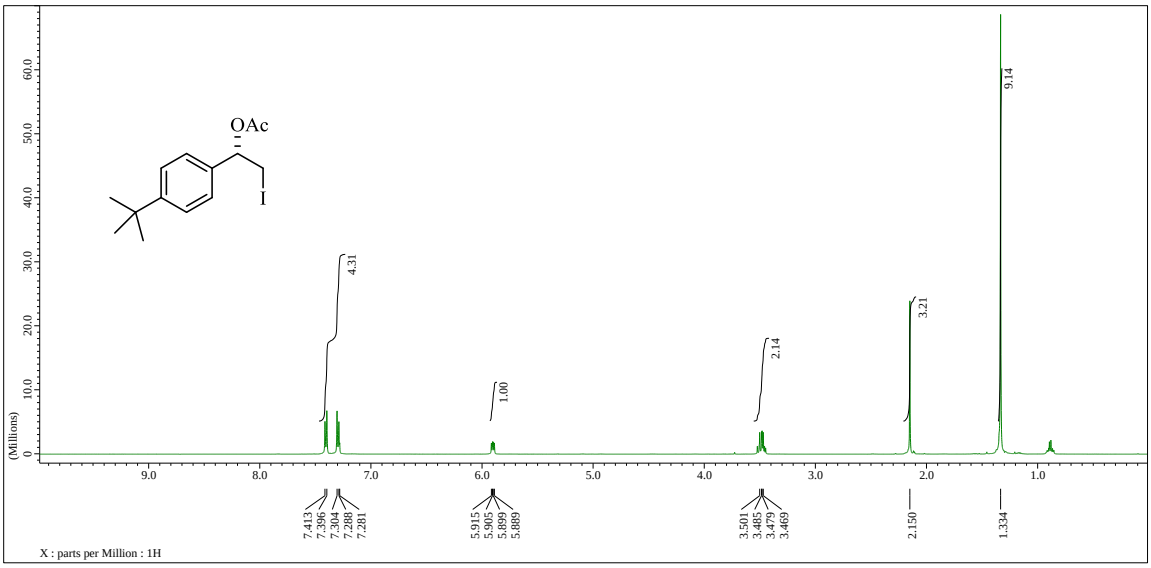

nBu
iPr
O
OEt
HO
(Thousands)
X : parts per Million : 13C

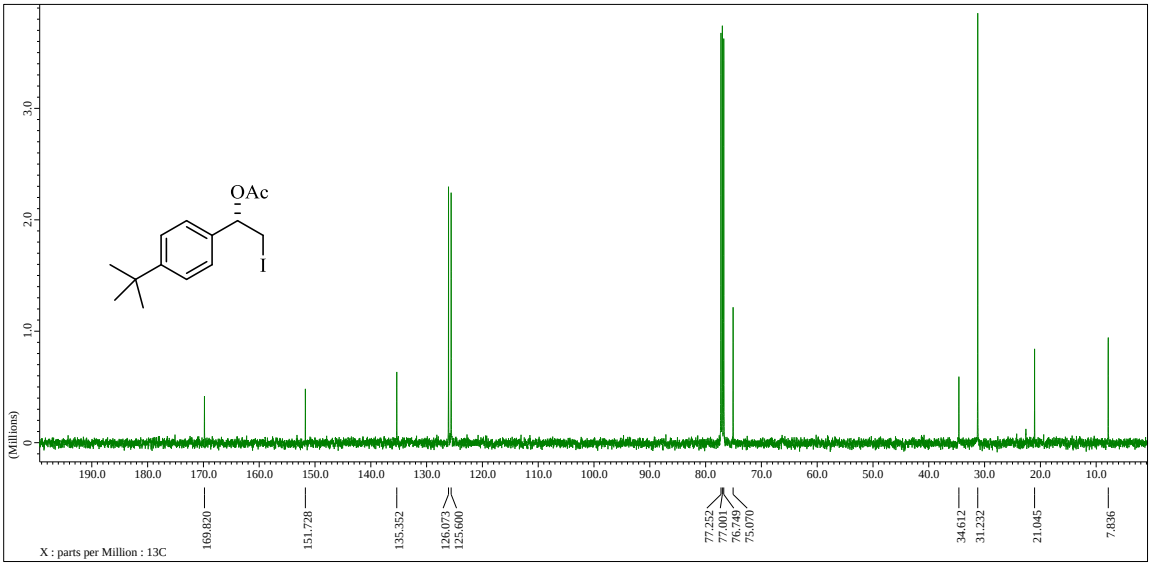

nBu
O
OEt
OH
iPr
(Millions)
X : parts per Million : 1H
7.282
5.621
4.276
4.268
4.262
4.255
4.250
4.240
4.235
4.226
4.222
4.214
4.207
4.200
2.375
2.057
2.028
2.023
1.688
1.677
1.316
1.302
1.287
0.955
0.945
0.932
0.917
0.903
0.901
0.886
0.851
1.00
2.03
8.15
8.00
9.04

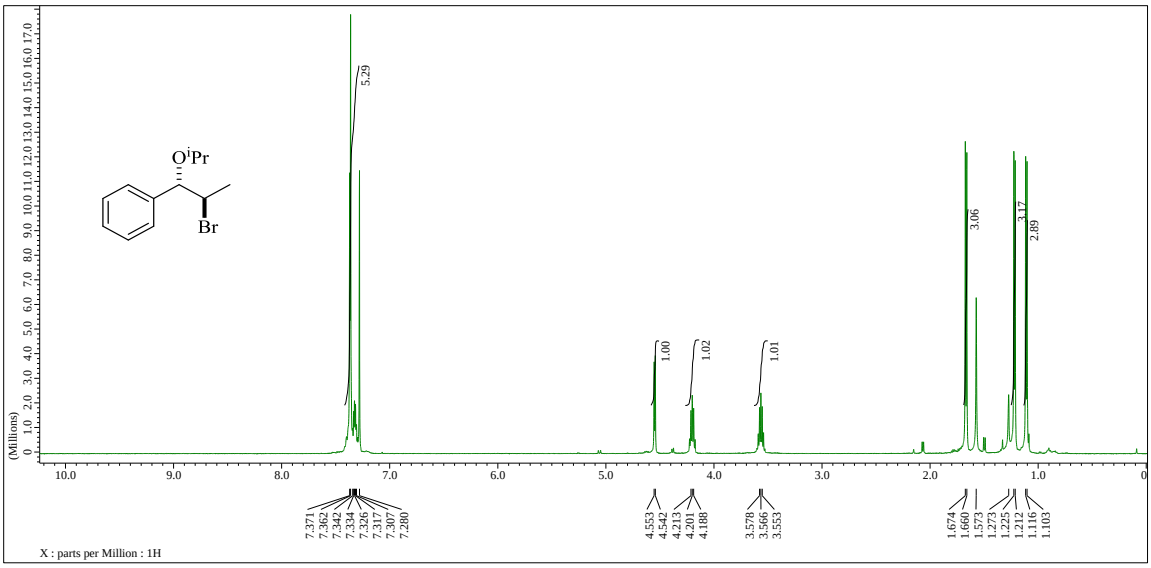

nBu
O
OEt
OH
iPr
(Thousands)
X : parts per Million : 13C
177.173
136.830
130.519
77.250
76.990
76.738
74.633
62.065
41.058
35.373
31.969
30.649
30.298
22.576
21.798
19.692
19.203
13.999

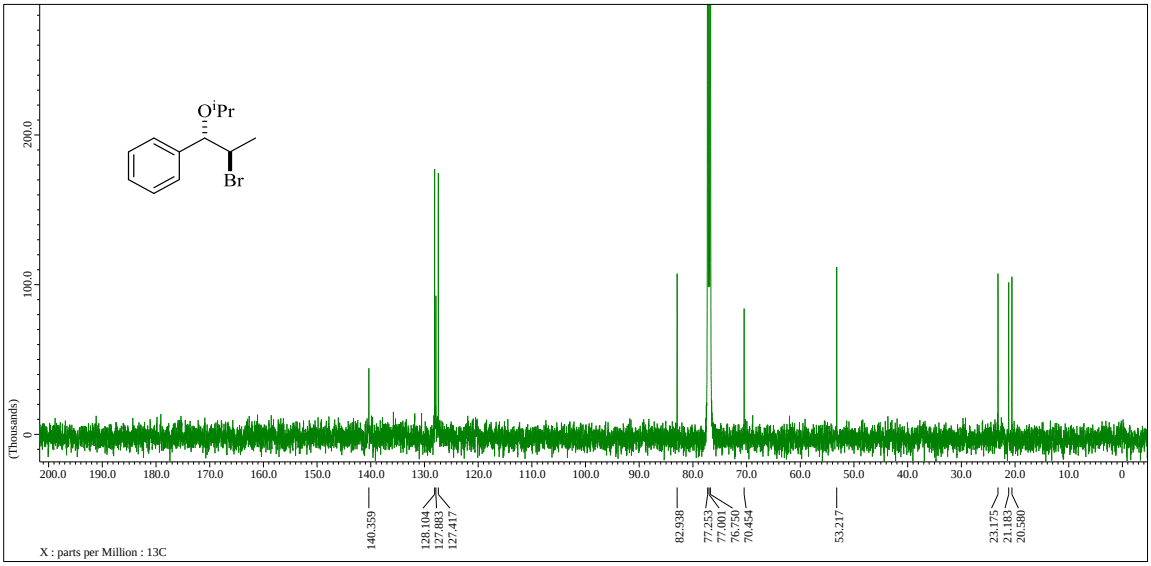

OAc
Br
(Millions)
30.0
20.0
10.0
0
4.24
1.00
2.12
2.99
9.22
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
7.420
7.404
7.314
7.297
7.280
6.008
5.999
5.991
5.983
3.693
3.676
3.672
3.655
3.619
3.610
3.597
2.153
1.333
X : parts per Million : 1H

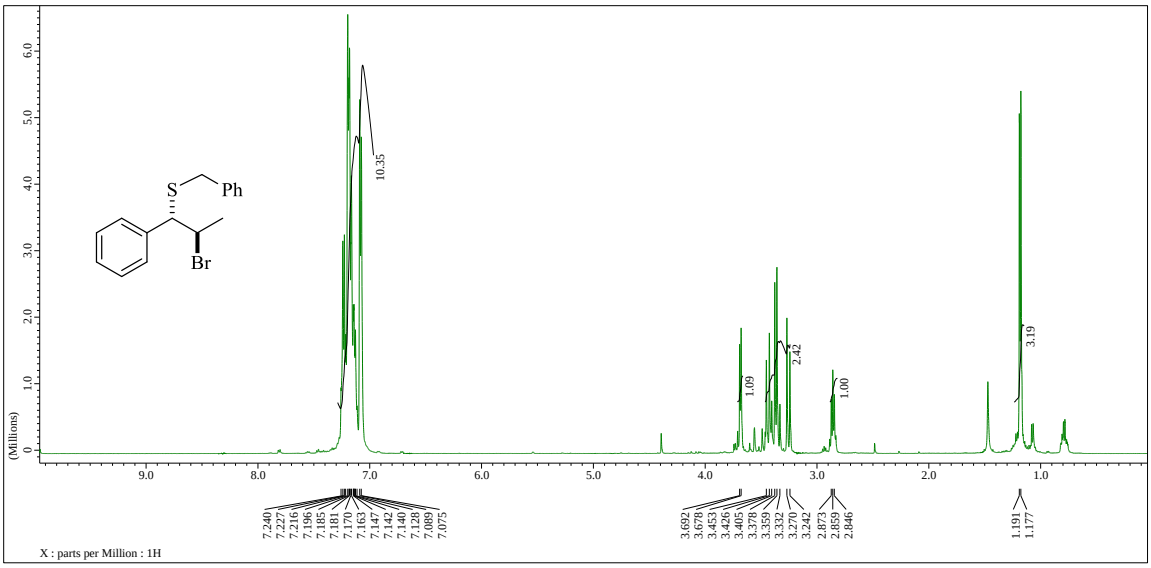

OAc
Br
(Millions)
2.0
1.0
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
169.883
151.844
134.614
126.274
125.625
77.247
76.995
76.743
74.721
34.607
34.300
31.234
21.002
X : parts per Million : 13C

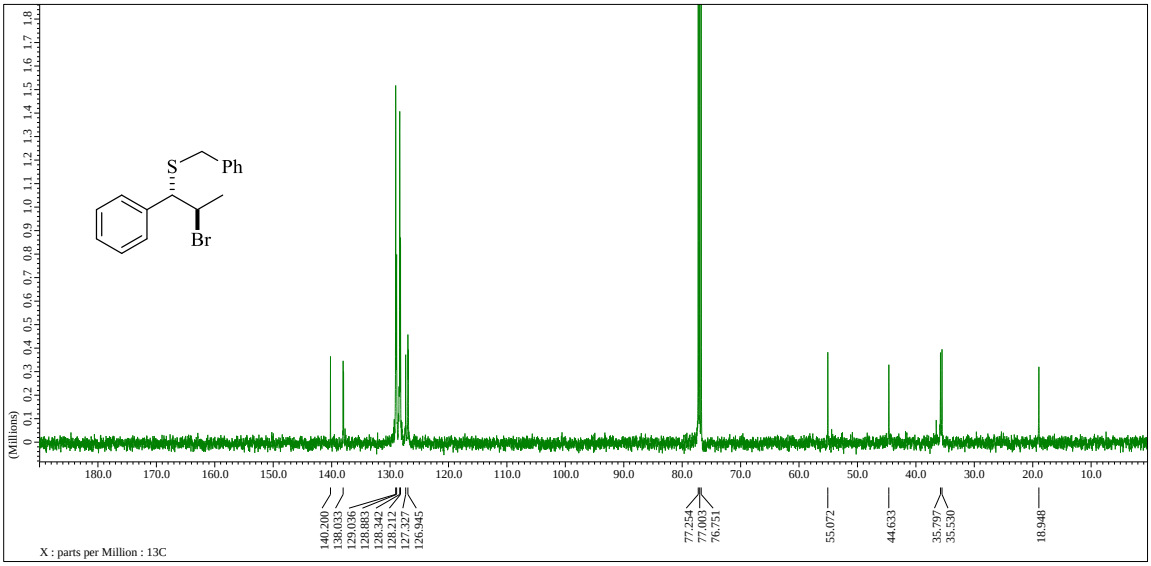

OAc
I
4.31
1.00
2.14
3.21
9.14
(Millions)
60.0
50.0
40.0
30.0
20.0
10.0
0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
7.413
7.396
7.304
7.288
7.281
5.915
5.905
5.899
5.889
3.501
3.485
3.479
3.469
2.150
1.334
X : parts per Million : 1H

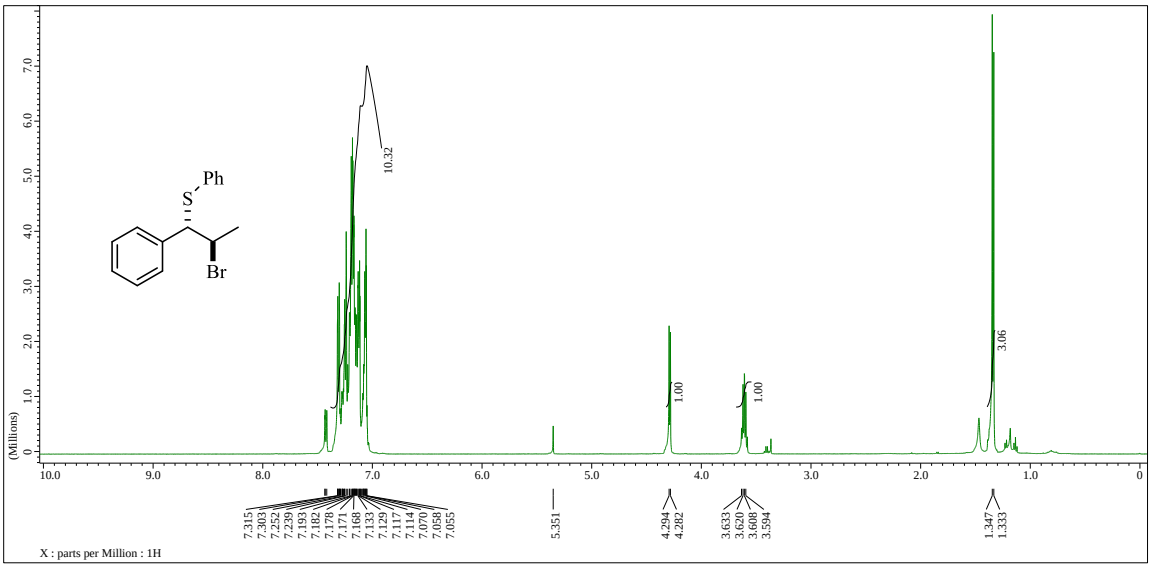

OAc
I
(Millions)
3.0
2.0
1.0
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
169.820
151.728
135.352
126.073
125.600
77.252
77.001
76.749
75.070
34.612
31.232
21.045
7.836
X : parts per Million : 13C

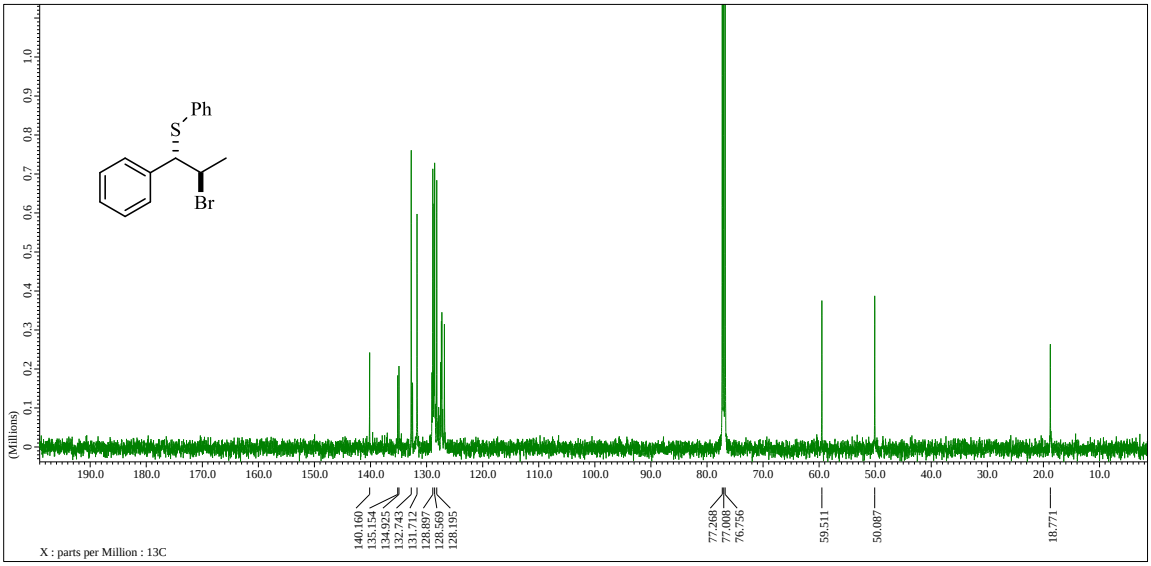

O^iPr
Br
(Millions)
5.29
1.00
1.02
1.01
3.06
3.17
2.89
7.371
7.362
7.342
7.334
7.326
7.317
7.307
7.280
4.553
4.542
4.213
4.201
4.188
3.578
3.566
3.553
1.674
1.660
1.573
1.273
1.225
1.212
1.116
1.103
X : parts per Million : 1H

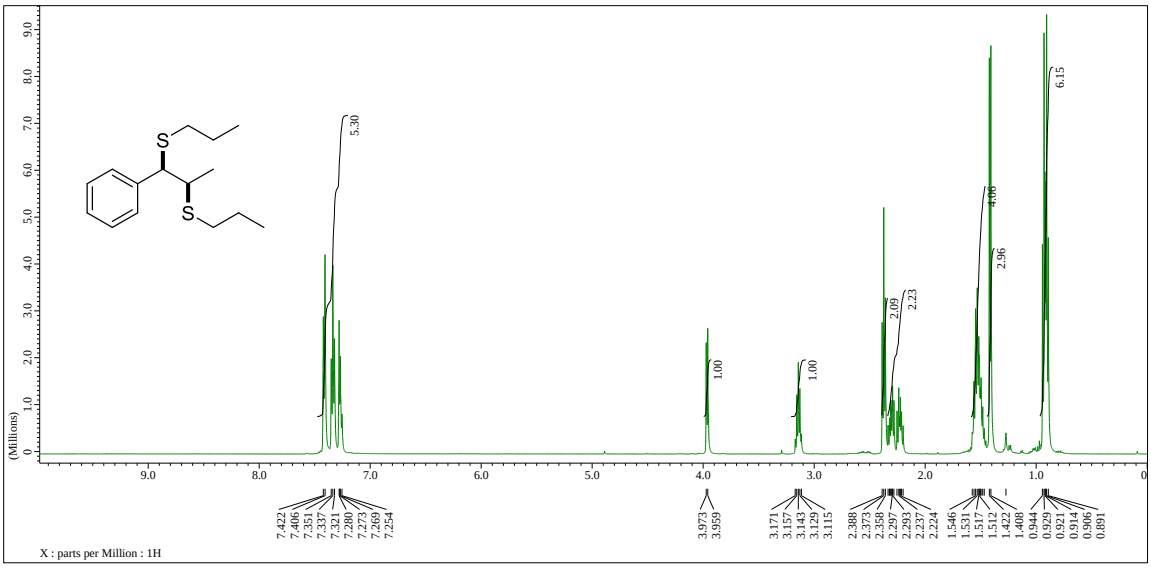

O^iPr
Br
(Thousands)
140.359
128.104
127.883
127.417
82.938
77.253
77.001
76.750
70.454
53.217
23.175
21.183
20.580
X : parts per Million : 13C

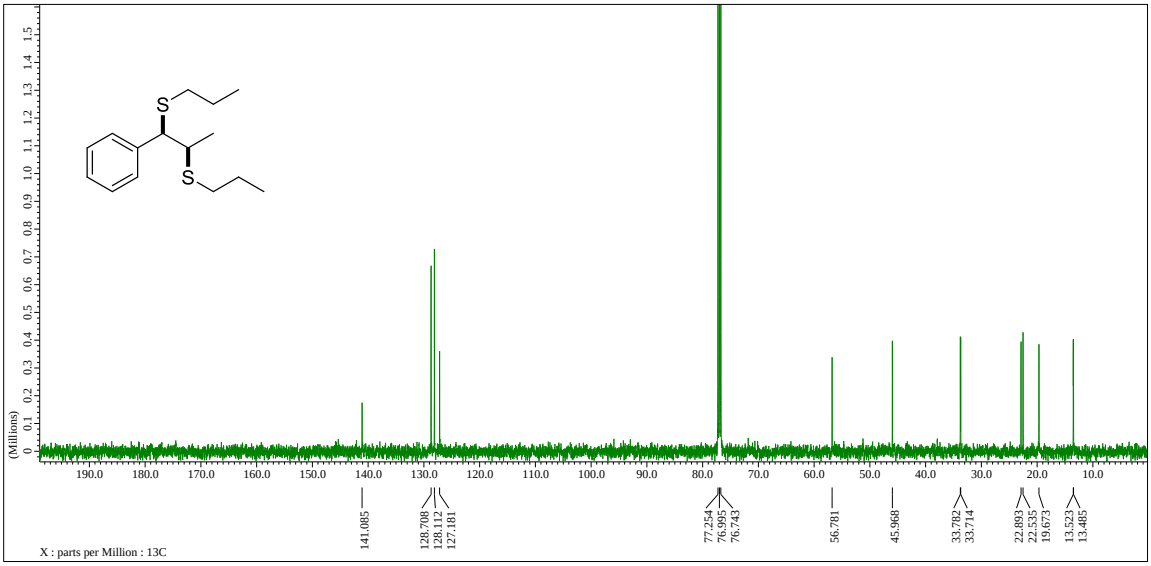

S
Ph
Br
10.35
1.09
2.42
1.00
3.19
(Millions)
X : parts per Million : 1H

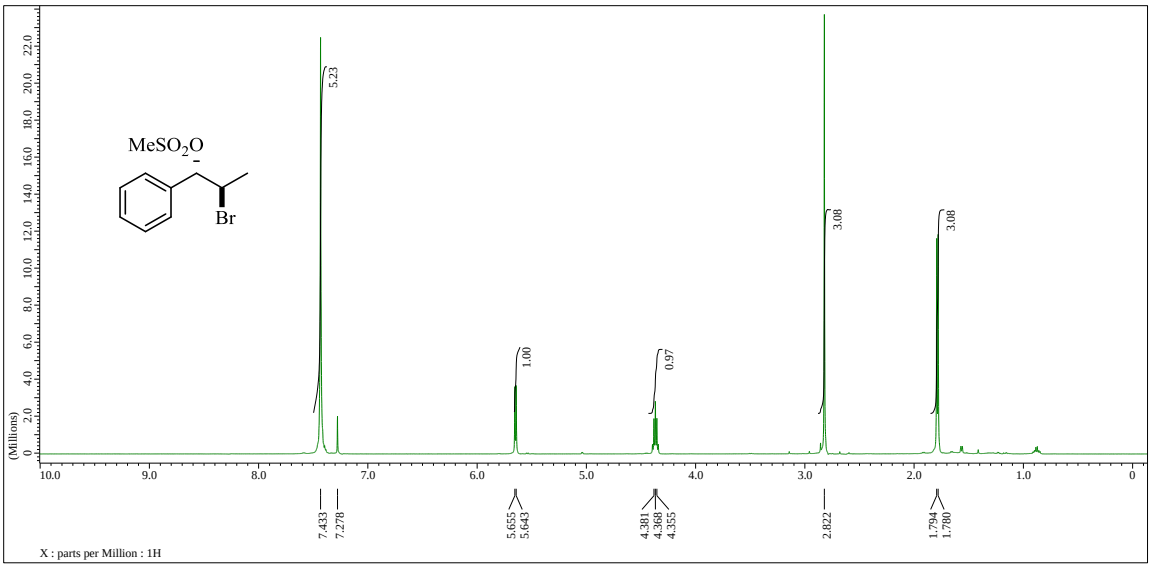

S
Ph
Br
(Millions)
X : parts per Million : 13C

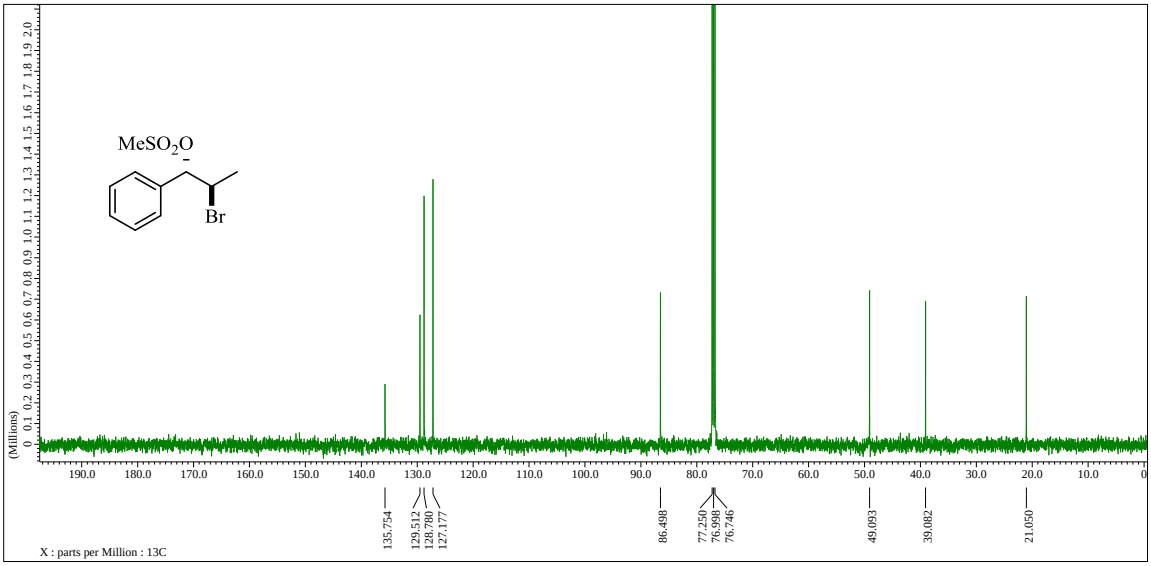

Ph
S
Br
10.32
1.00
1.00
3.06
(Millions)
7.315
7.303
7.252
7.239
7.193
7.182
7.178
7.171
7.168
7.133
7.129
7.117
7.114
7.070
7.058
7.055
5.351
4.294
4.282
3.633
3.620
3.608
3.594
1.347
1.333
X : parts per Million : 1H

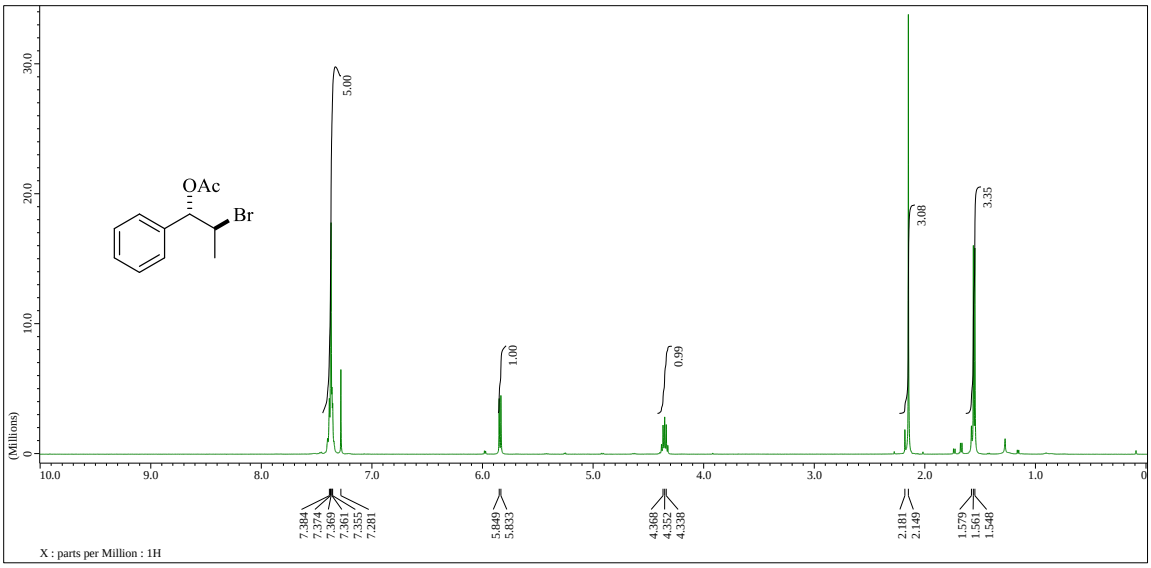

Ph
S
Br
(Millions)
140.160
135.154
134.925
132.743
131.712
128.897
128.569
128.195
77.268
77.008
76.756
59.511
50.087
18.771
X : parts per Million : 13C

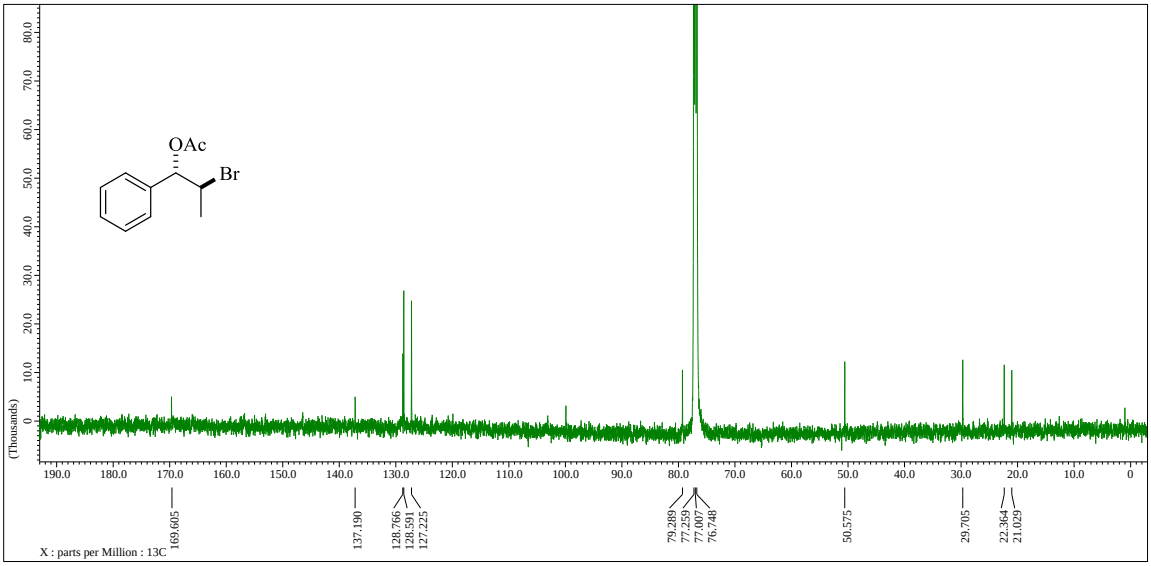

S
S
5.30
6.15
4.66
2.96
2.09
2.23
1.00
1.00
(Millions)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.422
7.406
7.351
7.321
7.280
7.273
7.269
7.254
3.973
3.959
3.171
3.157
3.143
3.129
3.115
2.388
2.373
2.358
2.297
2.293
2.237
2.224
1.546
1.531
1.517
1.512
1.422
1.408
0.944
0.929
0.921
0.914
0.906
0.891
X : parts per Million : 1H

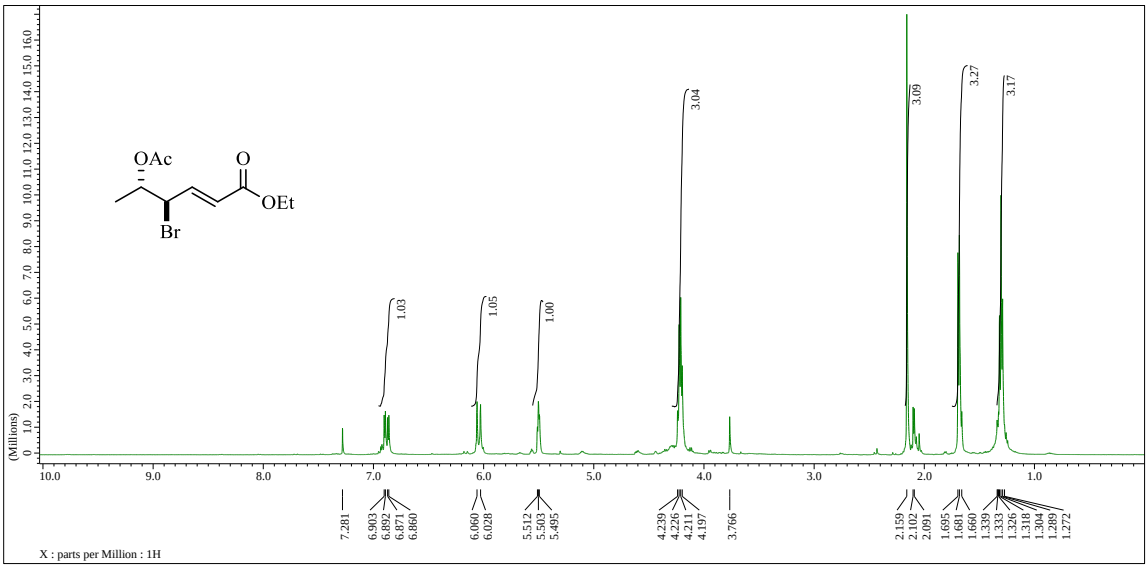

S
S
(Millions)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
141.085
128.708
128.112
127.181
77.254
76.995
76.743
56.781
45.968
33.782
33.714
22.893
22.535
19.673
13.523
13.485
X : parts per Million : 13C

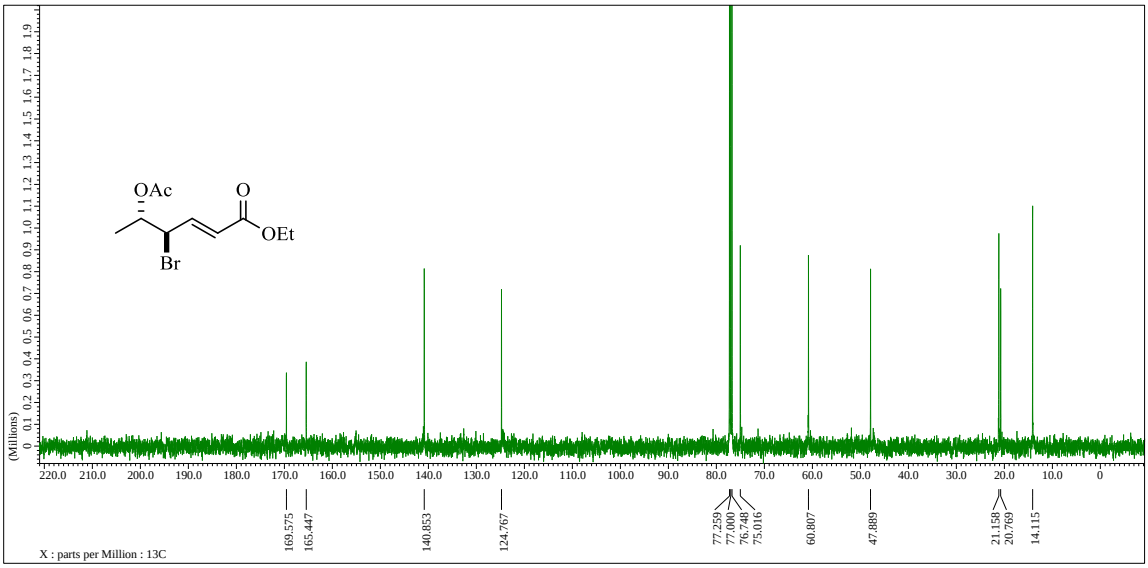

MeSO2O
Br
5.23
3.08
3.08
1.00
0.97
(Millions)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.433
7.278
5.655
5.643
4.381
4.368
4.355
2.822
1.794
1.780
X : parts per Million : 1H

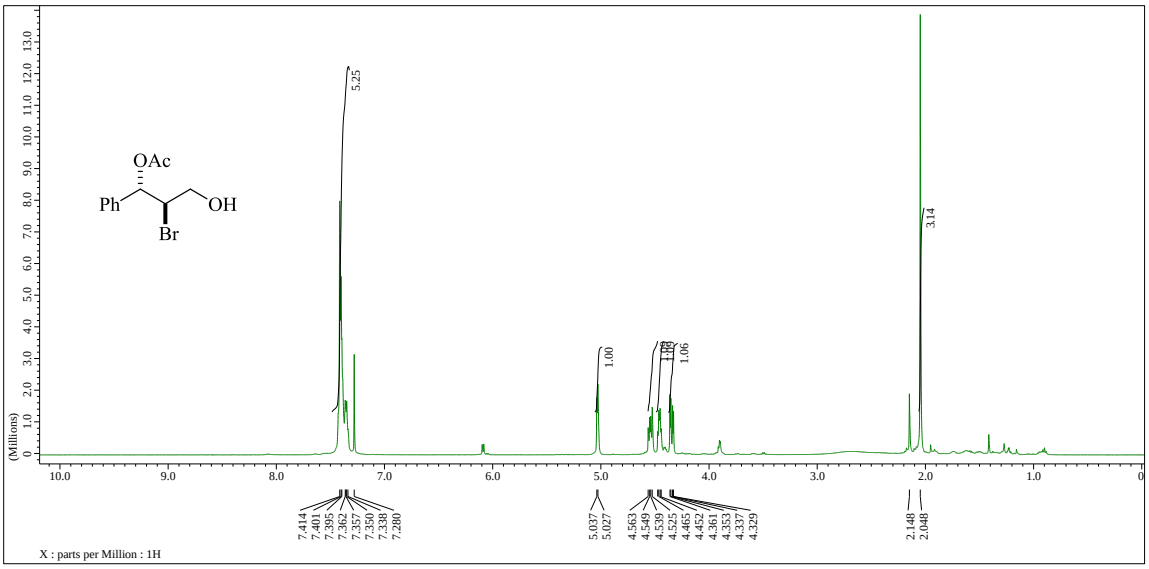

MeSO2O
Br
(Millions)
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
135.754
129.512
128.780
127.177
86.498
77.250
76.998
76.746
49.093
39.082
21.050
X : parts per Million : 13C

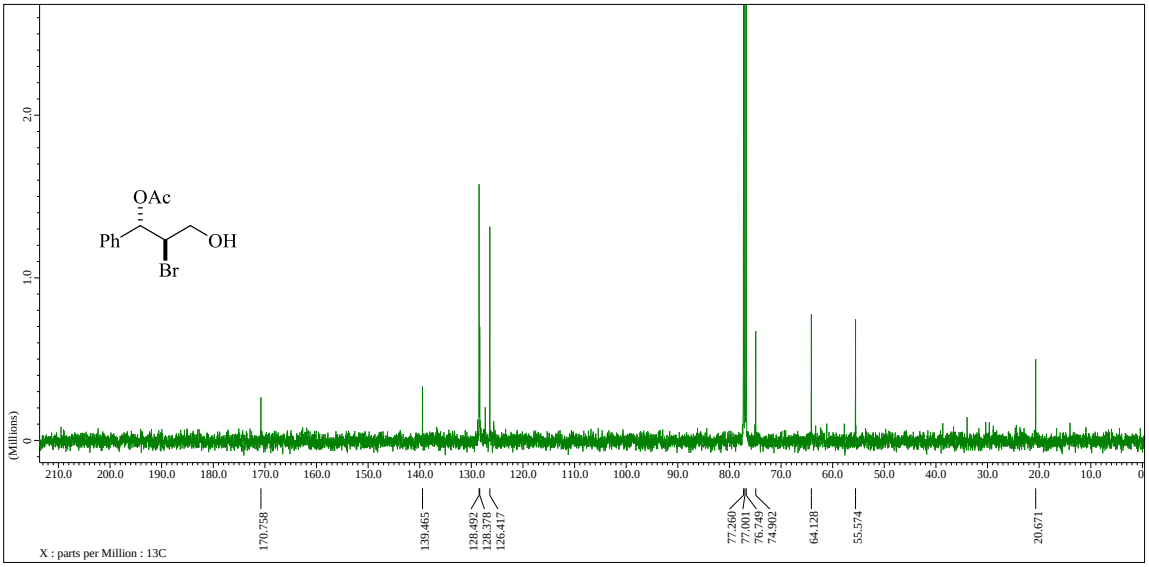

OAc
Br
5.00
1.00
0.99
3.08
3.35
(Millions)
7.384
7.374
7.369
7.361
7.355
7.281
5.849
5.833
4.368
4.352
4.338
2.181
2.149
1.579
1.561
1.548
X : parts per Million : 1H

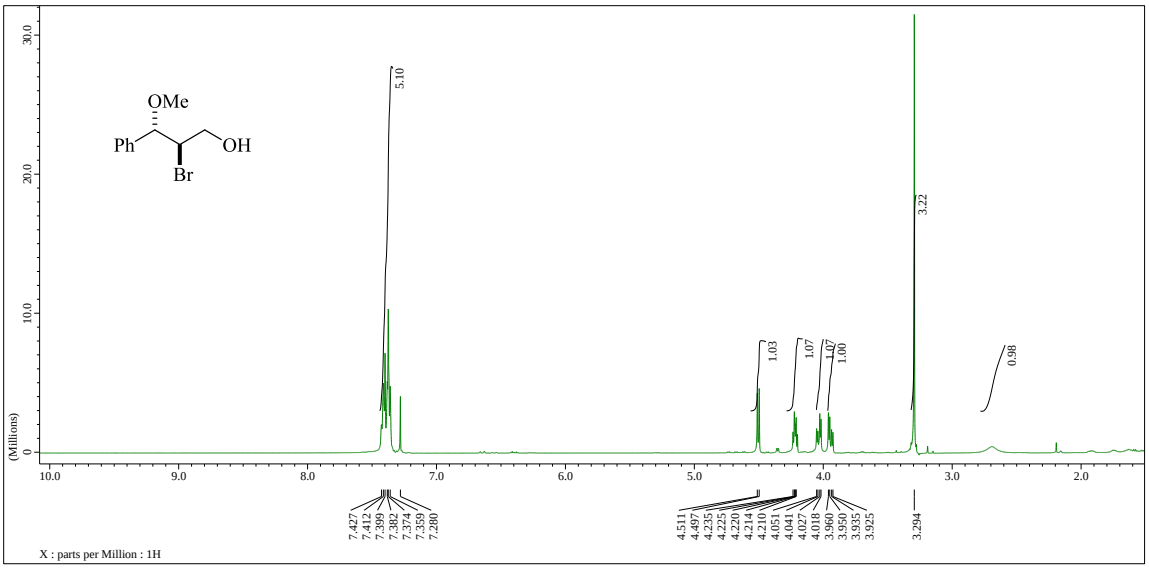

OAc
Br
(Thousands)
169.605
137.190
128.766
128.591
127.225
79.289
77.259
77.007
76.748
50.575
29.705
22.364
21.029
X : parts per Million : 13C

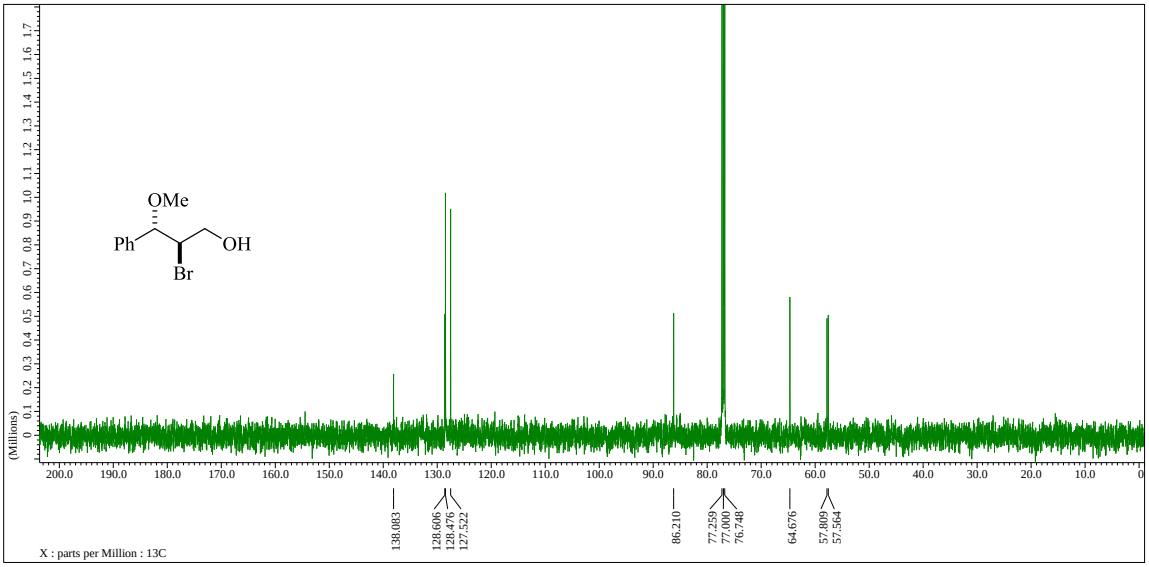

OAc
O
OEt
Br
1.03
1.05
1.00
3.04
3.09
3.27
3.17
(Millions)
7.281
6.903
6.892
6.871
6.860
6.060
6.028
5.512
5.503
5.495
4.239
4.226
4.211
4.197
3.766
2.159
2.102
2.091
1.695
1.681
1.660
1.339
1.333
1.326
1.318
1.304
1.289
1.272
X : parts per Million : 1H

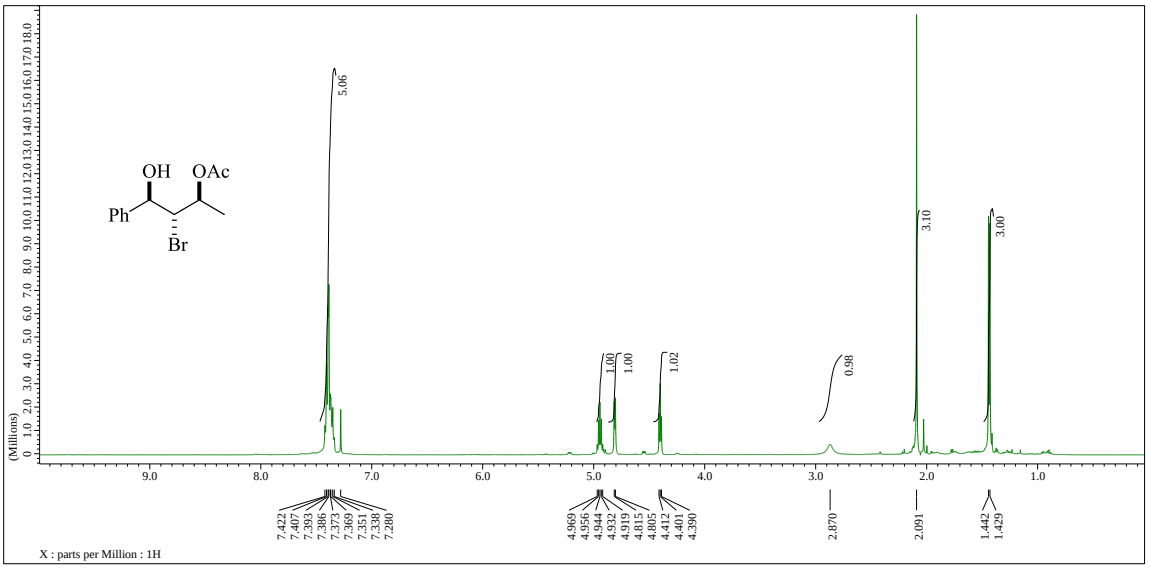

OAc
O
OEt
Br
(Millions)
169.575
165.447
140.853
124.767
77.259
77.000
76.748
75.016
60.807
47.889
21.158
20.769
14.115
X : parts per Million : 13C

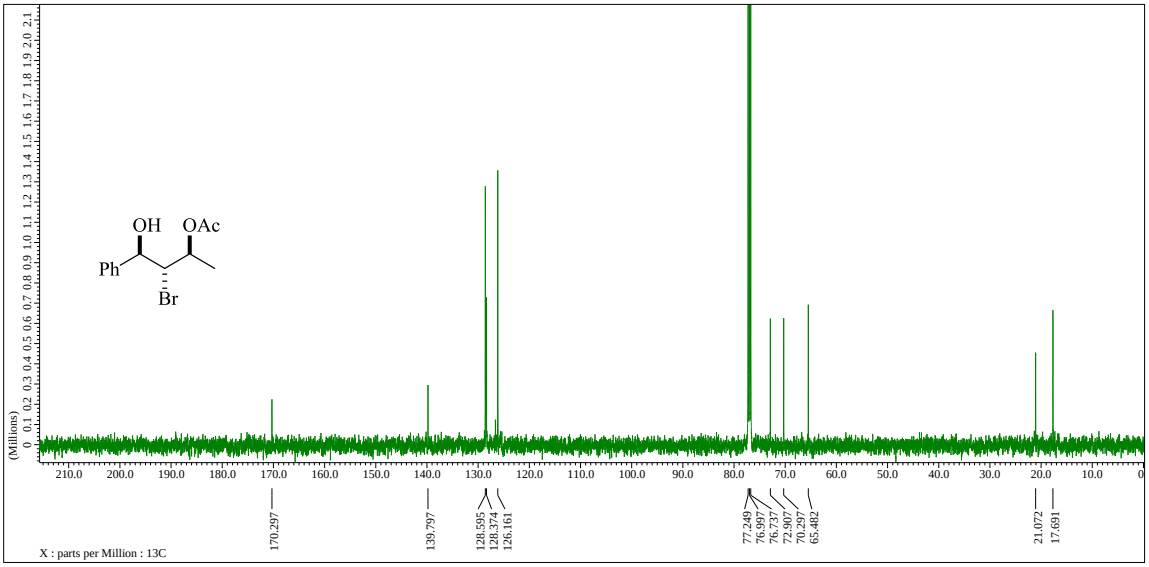

OAc
Ph
OH
Br
5.25
3.14
1.00
1.06
(Millions)
7.414
7.401
7.395
7.362
7.357
7.350
7.338
7.280
5.037
5.027
4.563
4.549
4.539
4.525
4.465
4.452
4.361
4.353
4.337
4.329
2.148
2.048
X : parts per Million : 1H

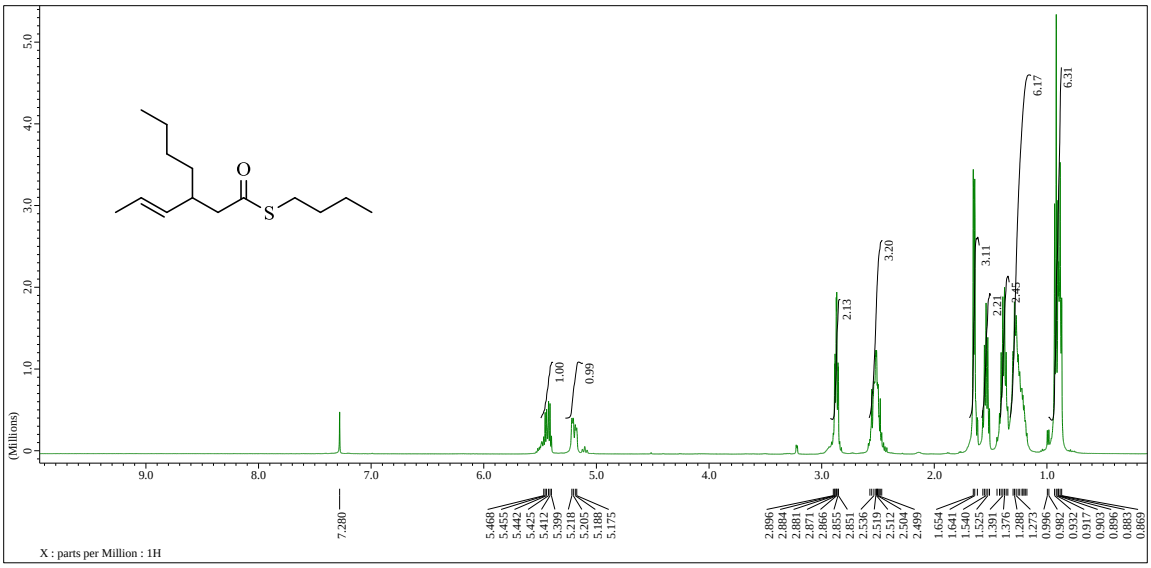

OAc
Ph
OH
Br
(Millions)
170.758
139.465
128.492
128.378
126.417
77.260
77.001
76.749
74.902
64.128
55.574
20.671
X : parts per Million : 13C

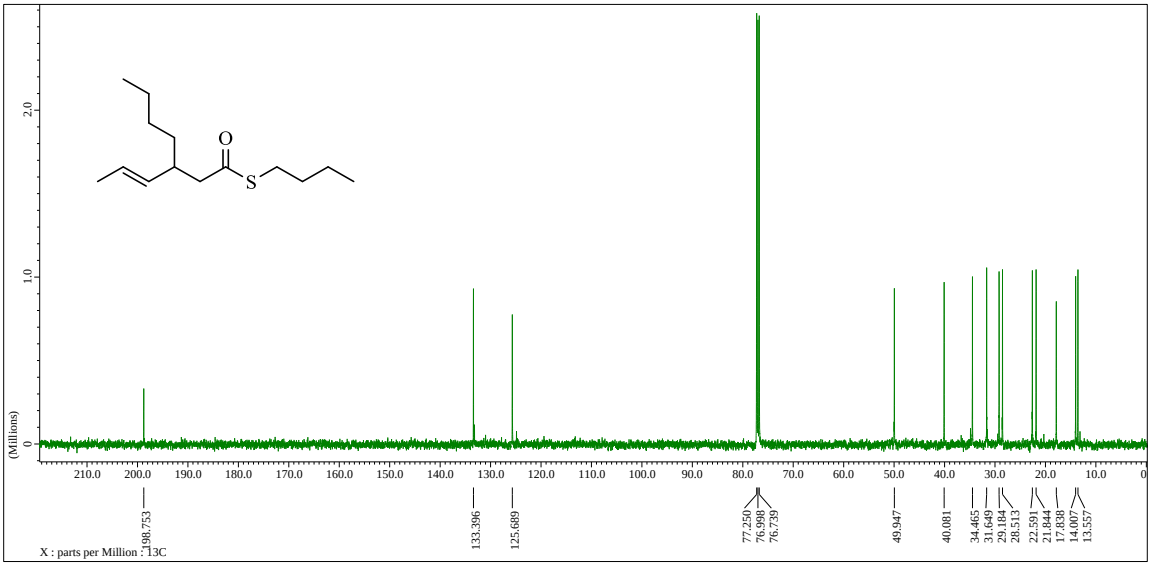

OMe
Ph
OH
Br
5.10
3.22
1.03
1.07
1.07
1.00
0.98
(Millions)
30.0
20.0
10.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
7.427
7.412
7.399
7.382
7.374
7.359
7.280
4.511
4.497
4.235
4.225
4.220
4.214
4.210
4.051
4.041
4.027
4.018
3.960
3.950
3.935
3.925
3.294
X : parts per Million : 1H

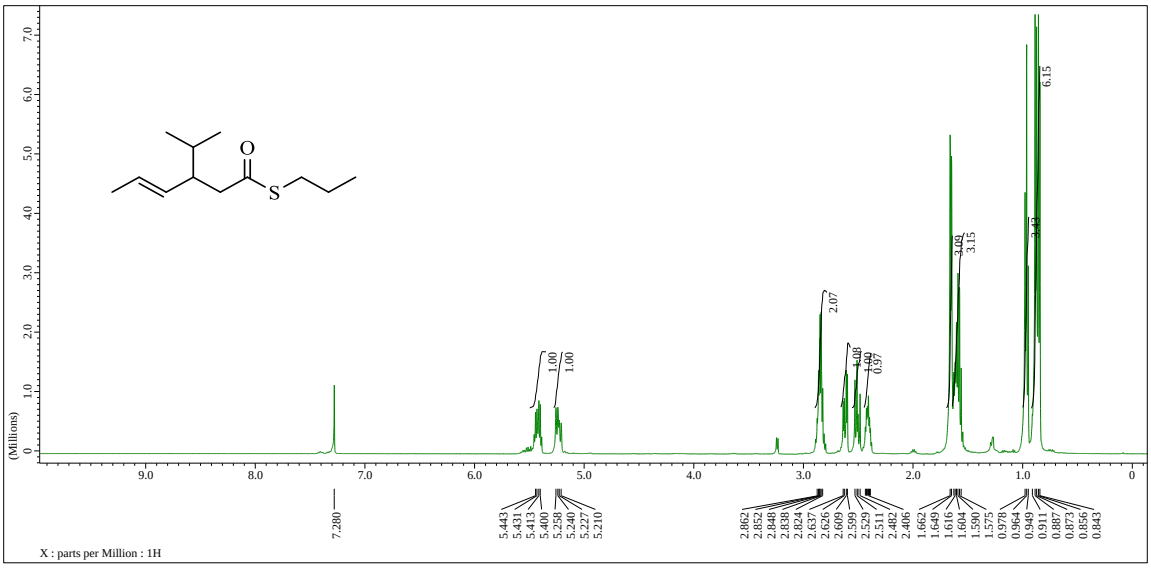

OMe
Ph
OH
Br
(Millions)
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
138.083
128.606
128.476
127.522
86.210
77.259
77.000
76.748
64.676
57.809
57.564
X : parts per Million : 13C

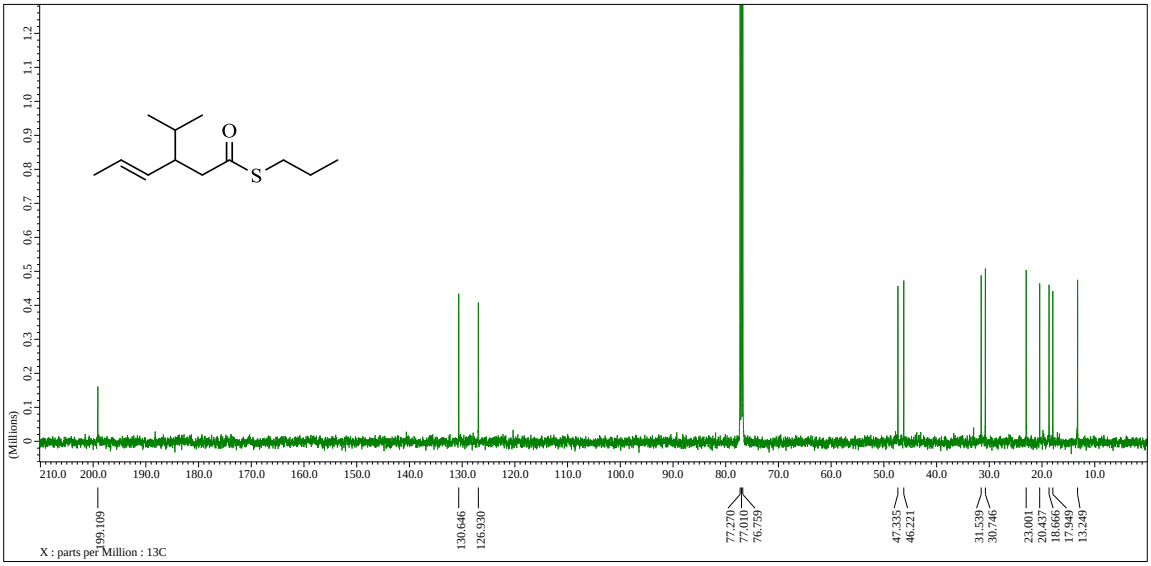

OH
OAc
Ph
Br
5.06
1.00
1.00
1.02
0.98
3.10
3.00
(Millions)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
7.422
7.407
7.393
7.386
7.375
7.369
7.351
7.338
7.280
4.969
4.956
4.944
4.932
4.919
4.815
4.805
4.412
4.401
4.390
2.870
2.091
1.442
1.429
X : parts per Million : 1H

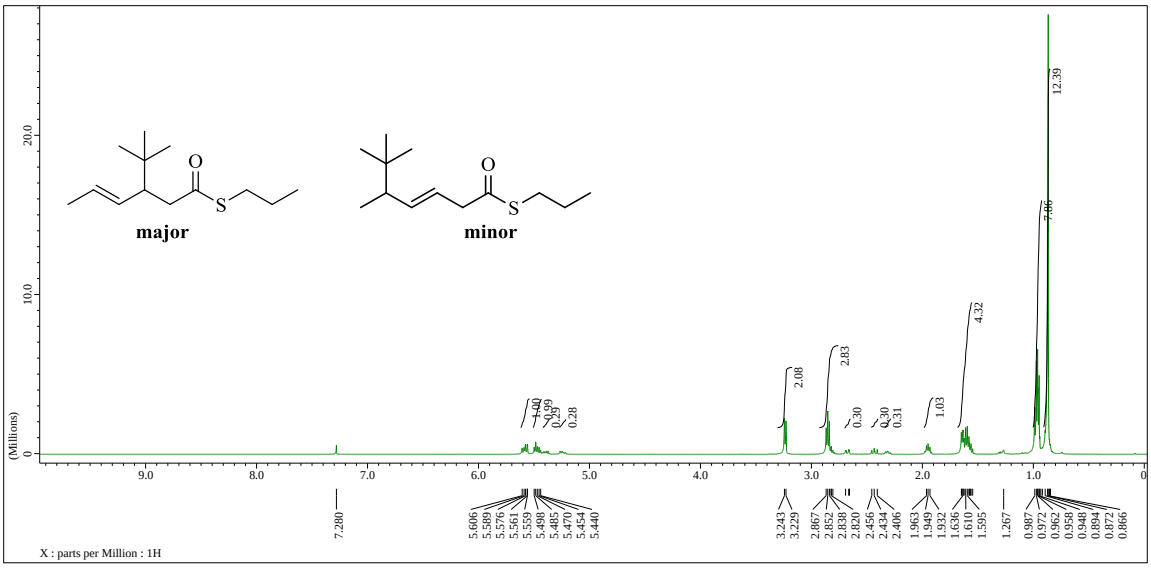

OH
OAc
Ph
Br
(Millions)
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
170.297
139.797
128.595
128.374
126.161
77.249
76.997
76.737
72.907
70.297
65.482
21.072
17.691
X : parts per Million : 13C

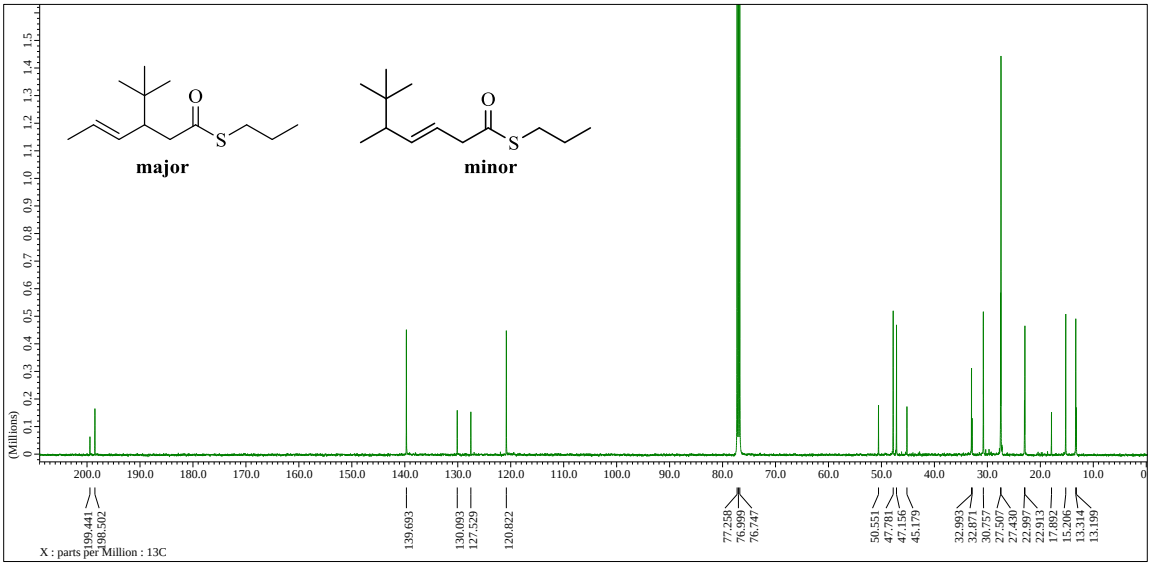

O
S
(Millions)
6.17
6.31
3.20
3.11
2.45
2.21
2.13
1.00
0.99
7.280
5.468
5.455
5.442
5.425
5.412
5.399
5.218
5.205
5.188
5.175
2.896
2.884
2.881
2.871
2.866
2.855
2.851
2.536
2.519
2.512
2.504
2.499
1.654
1.641
1.628
1.525
1.393
1.376
1.288
1.273
0.996
0.982
0.932
0.917
0.903
0.896
0.883
0.869
X : parts per Million : 1H

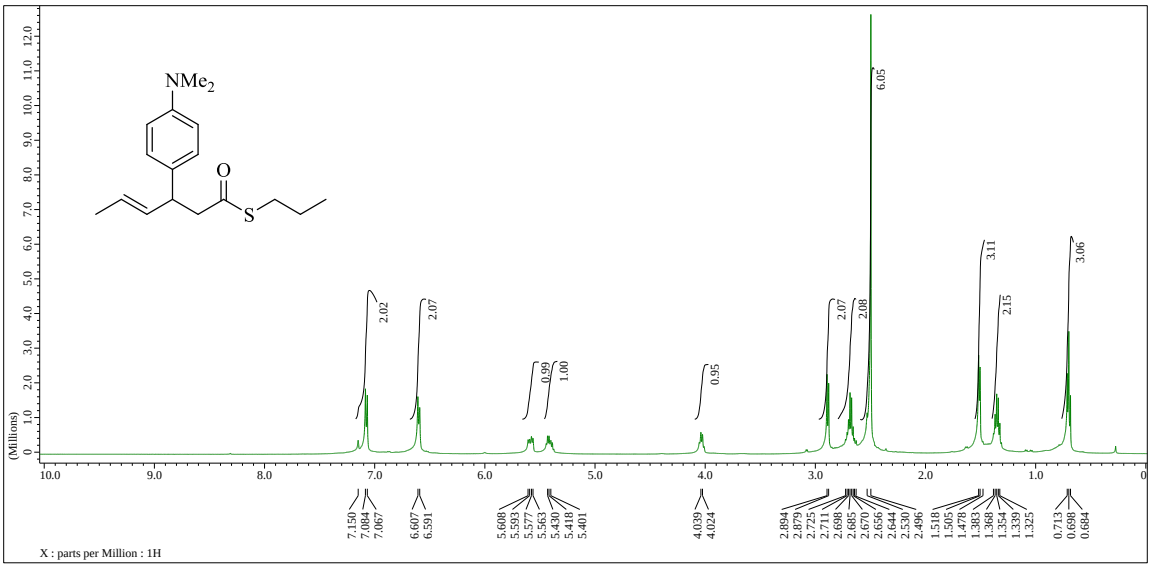

O
S
(Millions)
198.753
133.396
125.689
77.250
76.998
76.739
49.947
40.081
34.465
31.649
29.184
28.513
22.591
21.844
17.838
14.007
13.557
X : parts per Million : 13C

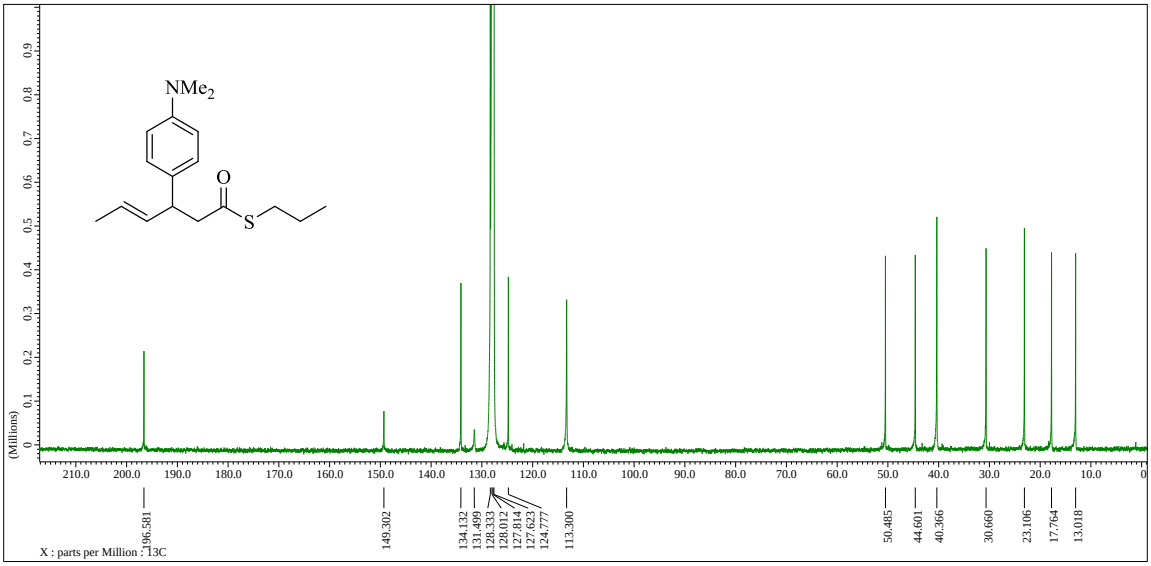

O
S
(Millions)
7.280
5.443
5.431
5.413
5.400
5.258
5.240
5.227
5.210
2.862
2.852
2.848
2.838
2.824
2.627
2.609
2.599
2.529
2.511
2.482
2.406
1.662
1.649
1.616
1.604
1.590
1.575
0.978
0.964
0.949
0.911
0.887
0.873
0.856
0.843
1.00
1.00
2.07
3.15
6.15
X : parts per Million : 1H

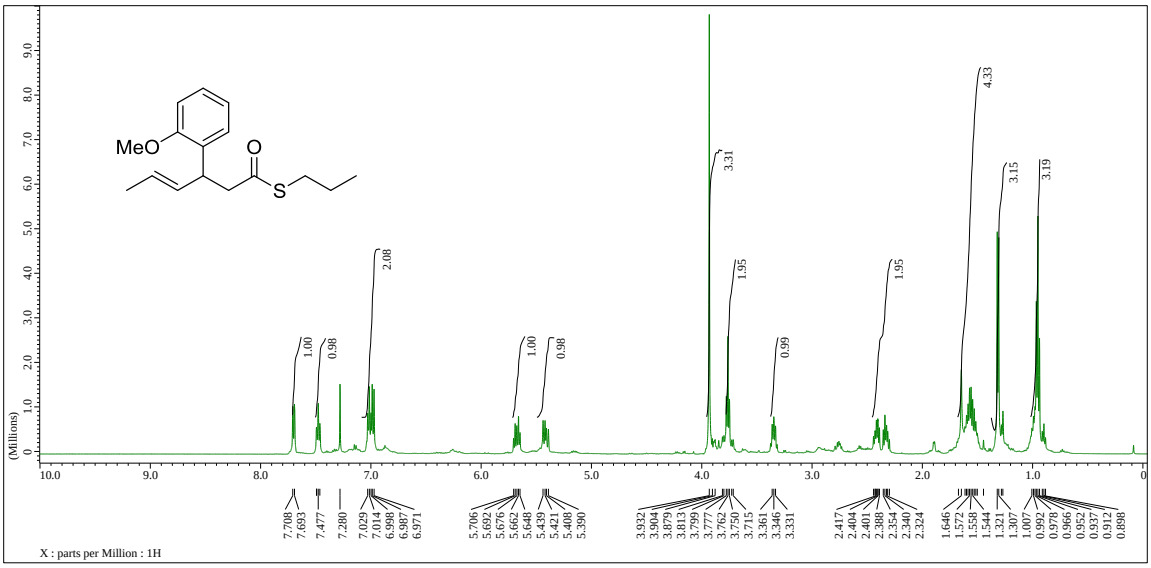

O
S
(Millions)
199.109
130.646
126.930
77.270
77.010
76.759
47.335
46.221
31.539
30.746
23.001
20.437
18.666
17.949
13.249
X : parts per Million : 13C

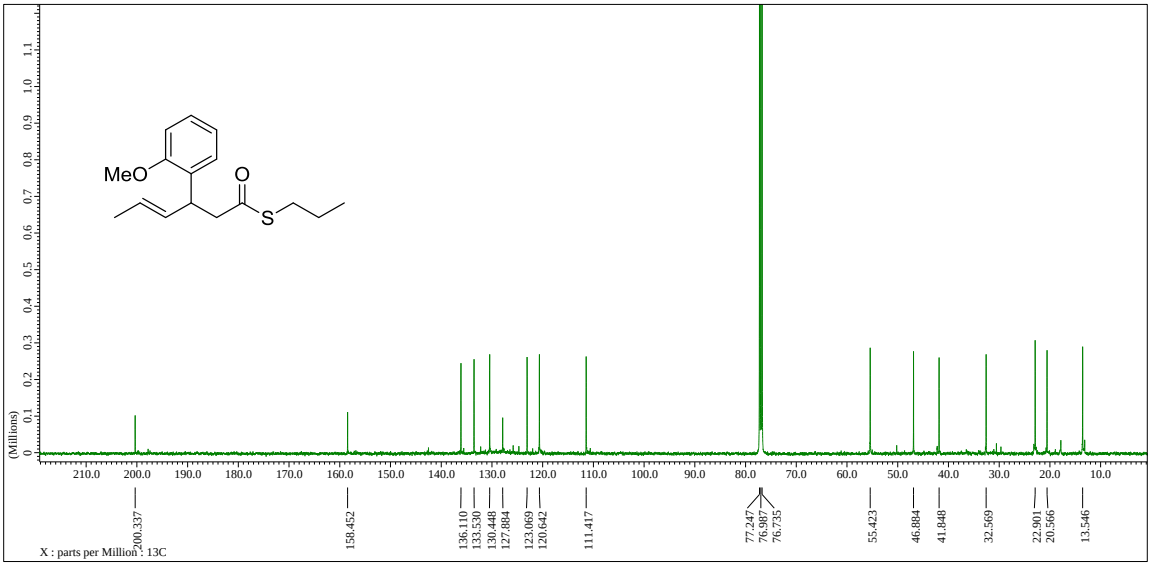

major
minor
12.39
7.86
4.32
2.83
2.08
1.03
0.30
0.30
0.31
0.28
(Millions)
X : parts per Million : 1H

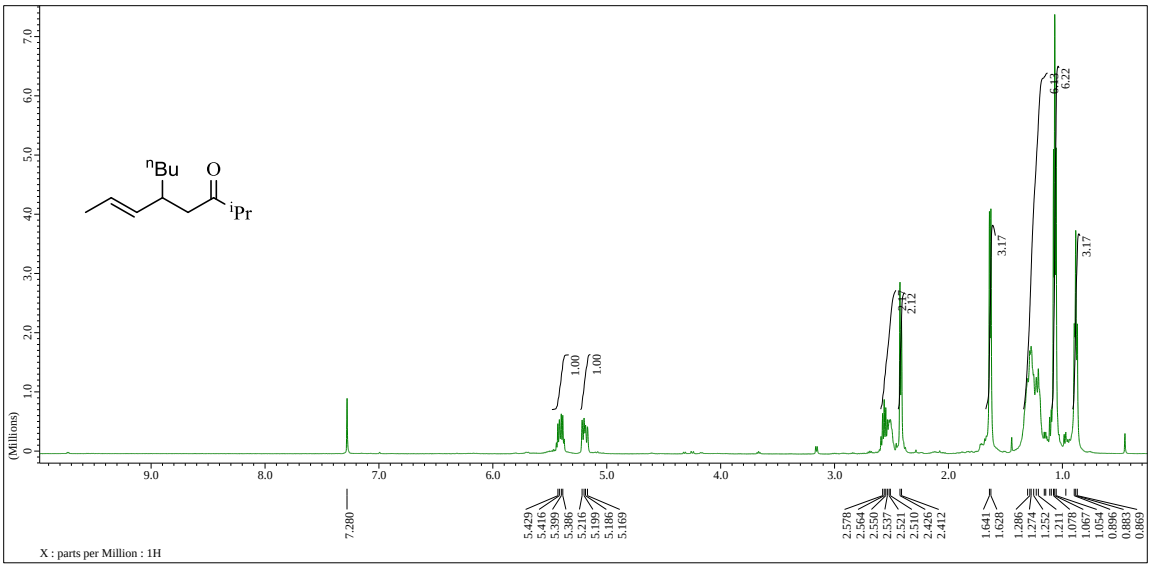

major
minor
(Millions)
X : parts per Million : 13C

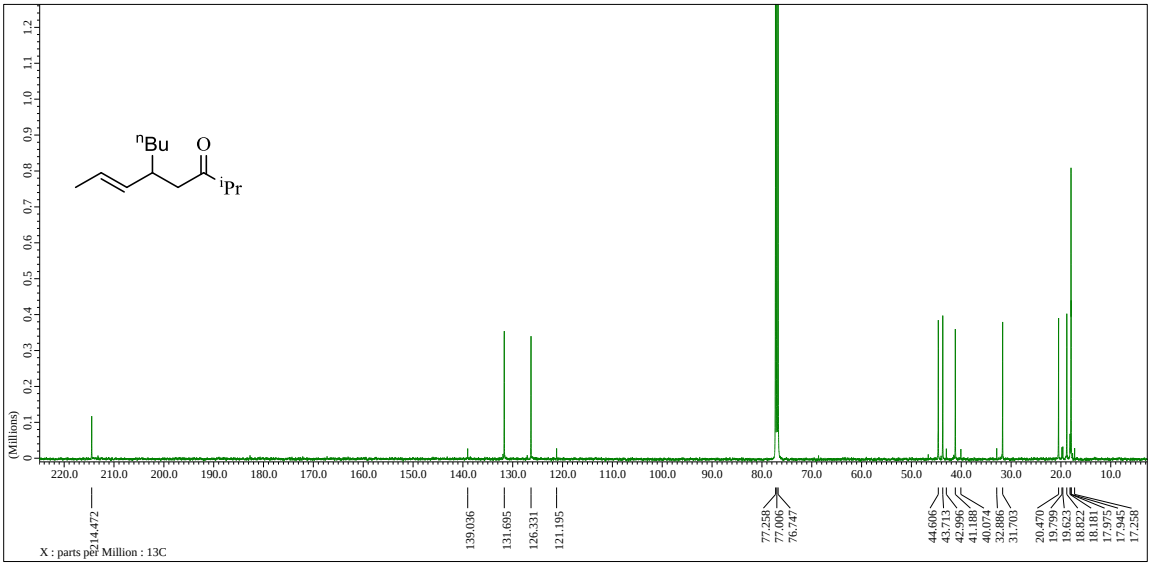

NMe2
O
S
(Millions)
2.02
2.07
0.98
1.00
0.95
6.05
2.07
2.08
3.11
2.15
3.06
7.150
7.084
7.067
6.607
6.591
5.608
5.593
5.577
5.563
5.430
5.418
5.401
4.039
4.024
2.894
2.879
2.725
2.711
2.698
2.685
2.670
2.656
2.644
2.530
2.496
1.518
1.505
1.478
1.383
1.368
1.354
1.339
1.325
0.713
0.698
0.684
X : parts per Million : 1H

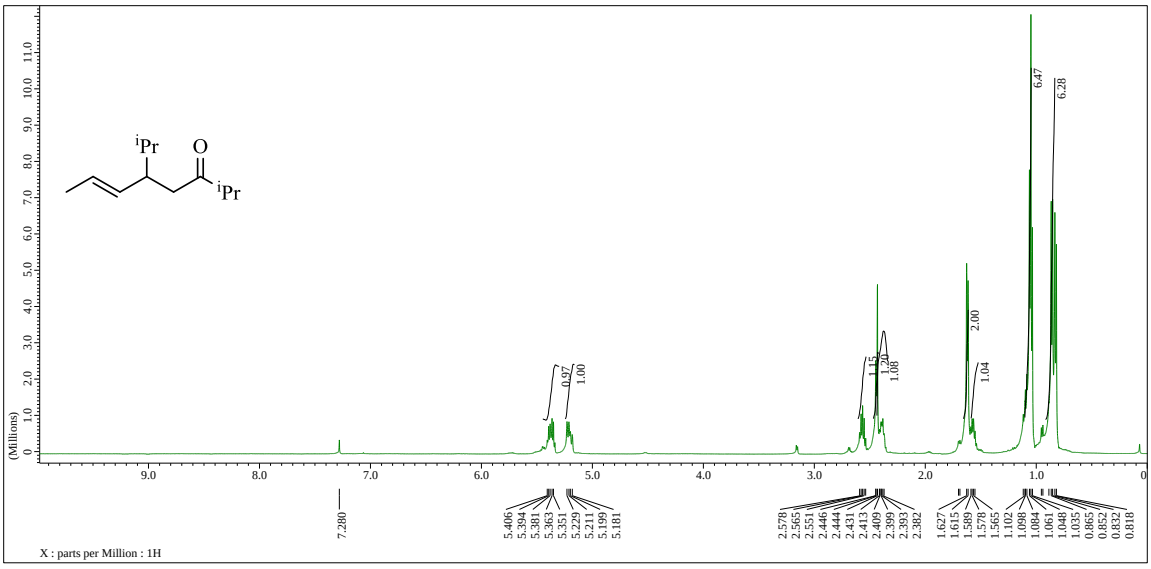

NMe2
O
S
(Millions)
196.581
149.302
134.132
131.499
128.333
128.012
127.814
127.623
124.777
113.300
50.485
44.601
40.366
30.660
23.106
17.764
13.018
X : parts per Million : 13C

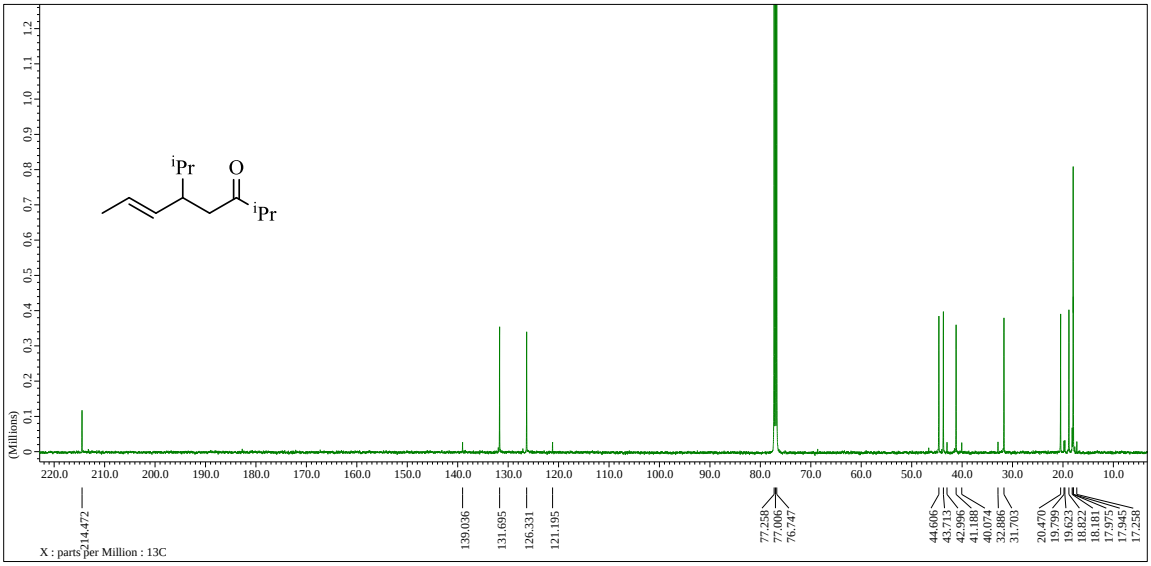

MeO
O
S
4.33
3.31
3.15
3.19
2.08
1.95
1.95
1.00
0.98
1.00
0.98
0.99
(Millions)
X : parts per Million : 1H

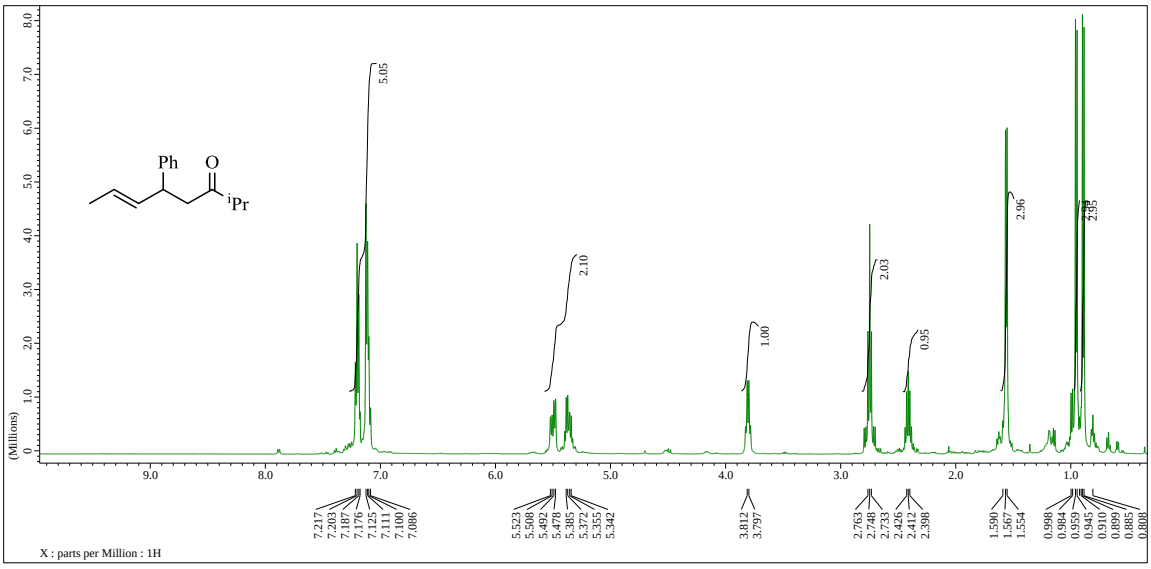

MeO
O
S
(Millions)
X : parts per Million : 13C

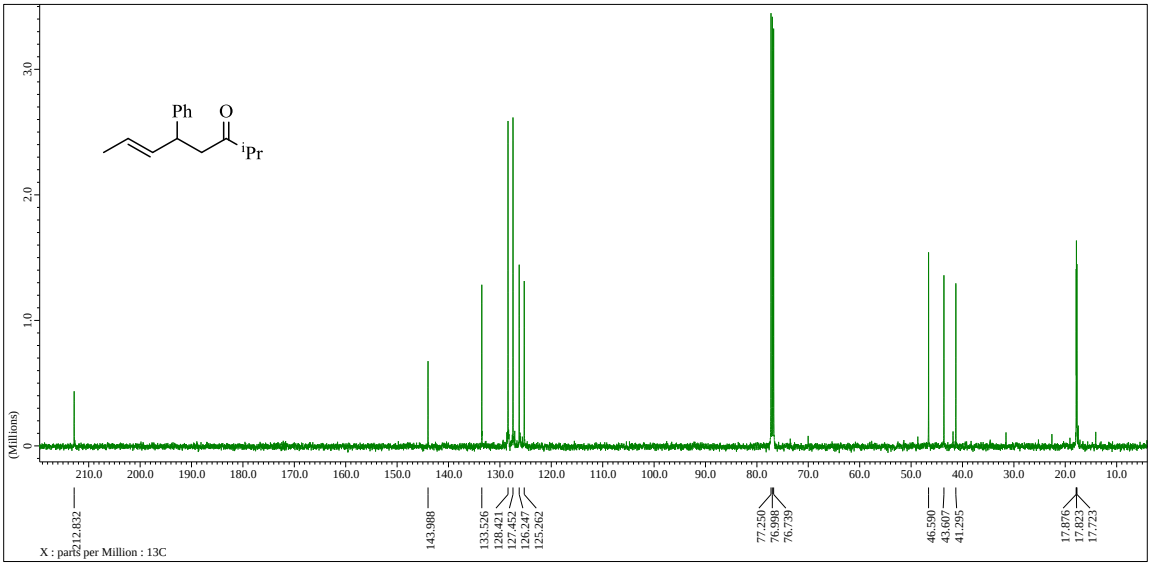

nBu
O
iPr
(Millions)
7.280
5.429
5.416
5.399
5.386
5.216
5.199
5.186
5.169
2.578
2.564
2.550
2.537
2.521
2.510
2.426
2.412
1.641
1.628
1.286
1.274
1.252
1.211
1.078
1.067
1.054
0.896
0.883
0.869
1.00
1.00
2.17
2.12
3.17
6.22
6.12
3.17
X : parts per Million : 1H


nBu
O
iPr
(Millions)
214.472
139.036
131.695
126.331
121.195
77.258
77.006
76.747
44.606
43.713
42.996
41.188
40.074
32.886
31.703
20.470
19.799
19.623
18.822
18.181
17.975
17.946
17.258
X : parts per Million : 13C


iPr
O
iPr
(Millions)
6.47
6.28
2.00
1.04
1.15
1.20
1.08
0.97
1.00
7.280
5.406
5.394
5.381
5.363
5.351
5.229
5.211
5.199
5.181
2.578
2.565
2.551
2.446
2.444
2.431
2.413
2.409
2.399
2.393
2.382
1.627
1.615
1.589
1.578
1.565
1.102
1.098
1.084
1.061
1.048
1.035
0.865
0.852
0.832
0.818
X : parts per Million : 1H


iPr
O
iPr
(Millions)
214.472
139.036
131.695
126.331
121.195
77.258
77.006
76.747
44.606
43.713
42.996
41.188
40.074
32.886
31.703
20.470
19.799
19.623
18.822
18.181
17.975
17.945
17.258
X : parts per Million : 13C


Ph
O
iPr
5.05
2.10
1.00
2.03
0.95
2.96
2.95
(Millions)
X : parts per Million : 1H


Ph
O
iPr
(Millions)
X : parts per Million : 13C